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American Heart Journal

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Original Communications

EXCRETION OF SODIUM-RETAINING SUBSTANCES IN PATIENTS WITH CONGESTIVE HEART FAILURE

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MONTREAL, P. Q.

IN RECENT years attention has been focused on the role of the kidney in the formation of edema in congestive heart failure.[1-7] It has been suggested that an endocrine mechanism, possibly involving the adrenal cortex, might play a role in the retention of salt and water in such clinical states.[1,8,9]

Thus far, the evidence for increased adrenal cortical activity in congestive heart failure has been scanty and controversial.[10-14] Parrish[10] found that four of ten patients with congestive failure had increased urinary adrenal cortical activity when studied by the survival time assay. Increased gluco-corticoid excretion was noted in all ten patients by the liver glycogen assay. Deming and Luetscher[11] were the first to report on the presence of urinary sodium-retaining substances in patients with congestive heart failure. These investigators, using an assay based on the total urinary sodium excretion of adrenalectomized animals, were able to show that five of six patients with uncompensated congestive failure, excreted significant quantities of sodium-retaining material. On the other hand, Lasche and associates[12] found a reduction in urinary formaldehydogenic corticoids and 17-ketosteroids in the majority of their patients with congestive heart failure. There was an increase in the excretion of these substances following injection of mercurial diuretics. ACTH, without mercurial diuretics, did not cause an increase in the urinary corticoids although a fall in eosinophils did occur. Their patients also had "hypoglycemic unresponsiveness" following a test dose of insulin, and the fall in eosinophils caused by this treatment was less than usual. These findings are in disagreement with the aforementioned results of Parrish.

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The present paper is a report on salt-retaining activity of urinary extracts in patients with congestive heart failure as compared to that found in normal individuals.

METHOD

The method used in this study has been described in detail elsewhere.[15] It is based on the effect of the administration of extracts of human urine on the excretion of a dose of sodium-24 by adrenalectomized rats under standard conditions.

The urines of thirteen normal persons and seven patients with varying degrees of congestive heart failure were collected for a 24-hour period. The patients with congestive heart failure were divided into two groups depending on their clinical condition at the time of urine collection. One group consisted of patients who showed evidence of marked retention of fluid (severe). The other group (controlled) were patients who had some residual dyspnea on exertion but no outward signs of edema. One patient, A.M., was studied while in the severe state with dependent edema, and six months later in a relatively controlled state. These patients were treated with digitalis and mercurial diuretics. Their sodium chloride intake was two to four grams of salt per day. The collection of the urine was commenced seventy-two hours after the last injection of a mercurial diuretic. All patients were ambulatory.

The twenty-four-hour urine volume was extracted with chloroform. The urine was acidified to pH 1.5 prior to extraction. After evaporation of the chloroform the residue was dissolved in a small quantity of absolute alcohol and stored in sealed ampules and refrigerated until they were assayed.

The test animals used in these experiments were hooded male rats weighing 160 to 170 grams at the time of adrenalectomy. They were kept on a standard diet of Purina Fox Chow. Drinking fluid following operation was saline on the first day, and distilled water on the second. Food and water were removed from the cages one hour before the animals were treated with the radioactive material.

Two days after the animals were adrenalectomized, each animal received subcutaneous injections of an extract of a twenty-minute urine sample in 0.1 ml. of absolute alcohol, and one milliter of an aqueous solution containing 3.5 mg. of sodium chloride, and a tracer quantity of sodium-24. Each extract was assayed in eight animals. At the same time, a control group of eight similarly prepared animals was injected with 0.1 milliliter of absolute alcohol and the radioactive salt solution. The urethra of each animal was then ligated, and the animals were returned to their cages. The test and control animals were evenly distributed throughout all the cages.

Five hours after receiving the radioactive sodium the animals were killed and their urine was removed from the bladders. The mean amount of sodium-24 in the urine of the control animals was considered as 100 per cent excretion. The mean excretion of radioactive sodium of the test animals was expressed as a percentage of that of the control animals. Values under 100 per cent indicate sodium retention. These values were compared to the effect of desoxycorticosterone (DCA) in the assay.

RESULTS

Normal Adults.—Results of studies on thirteen normal adults are presented in Table I. The group consists of eight men and five women between the ages of 20 and 35. The mean sodium-24 excretion of the test animals was 102 per cent of that of the control animals. Although there was a greater excretion of radioactive sodium in the animals treated with female urine, the results are not significantly different from those observed in animals treated with male urine. The normal urine having the greatest activity (H.R.) produced a sodium-retention equivalent to that obtained with 1.8 γ of D.C.A.

TABLE I. EFFECT OF URINARY EXTRACTS OF NORMAL ADULTS ON THE URINARY EXCRETION OF SODIUM-24 IN RATS

SUBJECT	URINARY Na-24* (% OF CONTROLS)
Women	
R. M.	117.0
R. C.	128.5
M. I.	116.5
Y. K.	98.8
L. S.	98.0
Average	111.9 $\pm$5.92**
Men	
R. S.	92.8
M. S.	105.8
H. R.	78.9
E. E.	98.0
F. J.	106.1
G. J.	92.7
W. W.	104.5
D. K.	92.6
Average	96.4 $\pm$3.27**
Over-all Average	102.4 $\pm$3.61**

*Sodium-24 excretion of control animals was considered as 100 per cent excretion. Values under 100 per cent indicate sodium retention.

**Standard error.

Congestive Heart Failure.—Eight assays have been performed on urine from seven patients. The results are presented in Table II. The urines of the patients in severe congestive failure had marked sodium-retaining effects in the assay. All of the effects were greater than the greatest effect obtained in the group of normal subjects. The average sodium-24 excretion of the test animals was 62.3 per cent of that of the control animals. The difference between these results and those obtained in normal adults (Fig. 1) is highly significant (P is > 0.001). In terms of approximate DCA equivalents, the average sodium retention produced by these extracts was equivalent to that produced by 3.3 γ of DCA.

The urines of the four patients who were in mild failure at the time of study did not have as marked sodium-retaining effects as were observed in patients with severe cardiac failure. The average sodium-24 excretion of the test animals in

TABLE II. SODIUM-RETAINING SUBSTANCES IN THE URINE OF PATIENTS WITH CONGESTIVE HEART FAILURE

SUBJECT	AGE	SEX	ETIOLOGY	URINE VOLUME (ml./24-hours)	NO. OF DAYS AFTER LAST DIURETIC	OTHER TREATMENT	URINARY Na-24* (% OF CONTROLS)	APPROXIMATE DCA EQUIVALENT
Severe:								
H. S.	29	F	RHD	270		Digitalis	57.7	
A. B.†	56	F	ASHD	2240		Digitalis	65.3	
A. M.	53	M	ASHD	525	3	Digitalis	64.1	
A. M.	61	M	HCVD	695	6	Digitalis	64.2	
						Average	62.3 ±1.72‡	3.3
Controlled:								
H. S.	60	M	RHD	750	7	Digitalis	89.0	
E. V.	53	M	ASHD	915	6	Digitalis and NH_4Cl	87.6	
L. M.	54	M	HCVD	1480	3	NH_4Cl	77.7	
A. M.	53	M	ASHD	600	3	Cation exchange resin	89.0	
						Average	85.8 ±2.73‡	1.0

*Sodium-24 excretion of control animals was considered as 100 per cent. Values under 100 per cent indicate sodium retention.
†Diabetic
‡Standard Error

this group of studies was 85.8 per cent of that of the control animals. In terms of approximate DCA equivalents the sodium retention produced by these extracts was similar to that caused by 1.0 γ of DCA. The effects of the urinary extracts obtained from this group (Fig. 1) of patients were significantly greater than those obtained from normal adults (P is >0.01).

It is of interest that patient A.M. (Table II) showed varied amounts of salt-retaining activity in his urine depending on the degree of congestive failure at the time of study. On one occasion when he was in severe failure, the bio-assay of his urine indicated that the test animals excreted only 64.2 per cent as much sodium-24 as the control animals. Six months later when the patient was relatively free of edema, the test animals with his urinary extract excreted 89.0 per cent as much sodium-24 as the control animals.

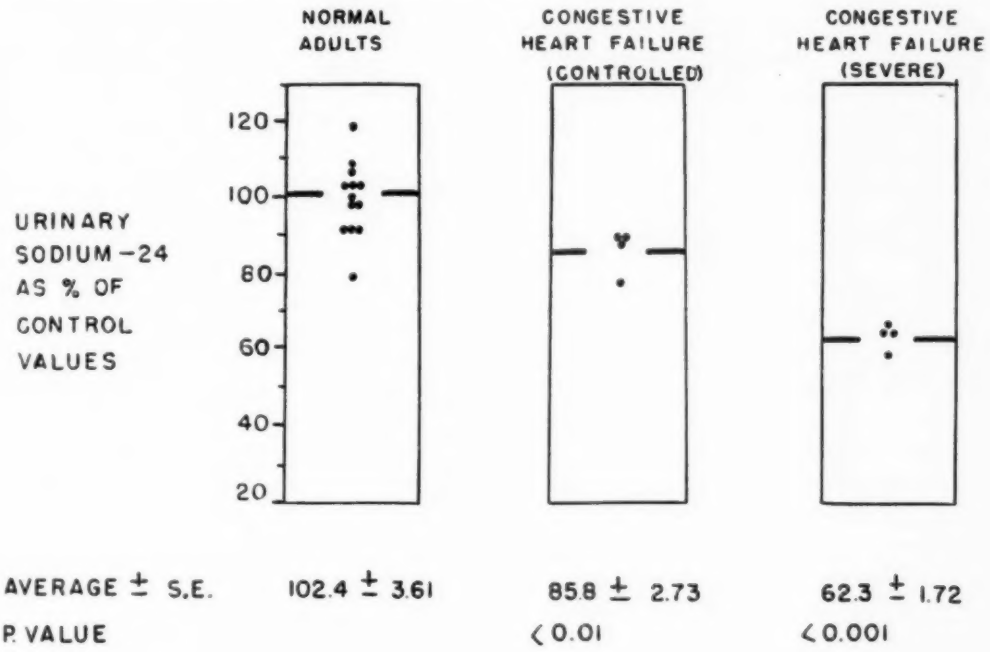

Fig. 1.—Effect of urinary extracts obtained from normal individuals and patients with congestive heart failure on the urinary excretion of radio-sodium in rats. An extract of a twenty minute sample of urine was used for each rat. Sodium-24 excretion of control animals was considered as 100 per cent. Values under 100 per cent indicate sodium retention. (*S.E.* = standard error.)

DISCUSSION

From the above data it is evident that there is a sodium-retaining activity in the urine of patients with congestive failure, particularly in the severe cases. The quantities of this substance found, roughly paralleled the degree of congestive failure present. These findings are in close agreement with those of Deming and Luetscher[11] who found with a similar method of assay increased quantities of urinary sodium-retaining substances in five of six patients with uncompensated heart failure.

Studies have shown that DCA can affect the transfer of sodium across the epithelium of the kidney, sweat glands, salivary glands, and the colon.[16-18] It has also been reported that in the edematous cardiac patient, as compared with the normal subject, there is a definite tendency to retain body sodium not only by the kidney tubules, but also by cell membranes of the sweat and salivary glands and the colon.[19-21] Recently, Reynolds[22] has found that sweat sodium concentrations are not reduced in patients with congestive heart failure but may in some instances be increased.

Bornstein and Trewhella[13] have reported that there was an increased ACTH activity in the plasma of six patients with congestive heart failure, which returned to normal levels following the control of the decompensation. Other observers have noted an increase in the antidiuretic "hormone" titers in the urine of patients with congestive heart failure.[14,23] Recently, as part of a study on the effect of growth hormone in human subjects,[24] it was found that there was a marked increase in the excretion of salt-retaining substances following the intravenous administration of growth hormone in two normal adults.

In other clinical conditions with edema, such as cirrhosis of the liver, there is a retention of fluid in the absence of disturbance of cardiac output or renal hemodynamics.[25] It is of interest that in patients with cirrhosis and nephrosis salt-retaining substances resembling DCA in action have also been detected in the urine.[26,27,28]

Clinically, the mechanisms of edema formation in patients with congestive failure have been explained on the basis of either the "backward failure" or the "forward failure" hypothesis. According to the former, the formation of edema is secondary to increased venous pressure due to the inability of the left ventricle to pump out the blood returned to it. The forward theory of congestive failure places the defect in the reduction of cardiac output resulting in a reduced renal plasma flow and glomerular filtration rate, which leads to impairment in excretion of sodium and water. The retention of salt and water by the kidney in patients with congestive failure has also been attributed to renal anoxia and increased renal venous pressure.[1-7] While it is agreed that these factors do influence the renal excretion of sodium in patients with heart failure, from the results of this present study and from the observations of others described above, it is becoming increasingly evident that overactivity of the adrenal cortex with increased secretion of the "mineralo-corticoids" may play a role in edema formation in many of the patients.

SUMMARY

1. An increased excretion of urinary salt-retaining substances has been found in patients with congestive heart failure by a biological assay procedure based on the urinary sodium-24 excretion of adrenalectomized rats.

2. The quantity of active material present was roughly proportional to the degree of failure present.

The authors wish to express sincere thanks to Dr. J. S. L. Browne and Dr. E. H. Venning for kind help, criticism, and encouragement throughout this investigation.

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REFERENCES

1. Warren, J. V., and Stead, E. A., Jr.: Fluid Dynamics in Chronic Congestive Heart Failure; Interpretation of Mechanisms Producing Edema, Increased Plasma Volume and Elevated Venous Pressure in Certain Patients With Prolonged Congestive Failure, Arch. Int. Med. **73**:138, 1944.
2. Merrill, A. J.: Edema and Decreased Renal Blood Flow in Patients With Chronic Congestive Heart Failure. Evidence of "Forward Failure" as the Primary Cause of Edema, J. Clin. Investigation **25**:389, 1946.
3. Mokotoff, R., Ross, G., and Leiter, L.: Renal Plasma Flow and Sodium Reabsorption and Excretion in Congestive Heart Failure, J. Clin. Investigation **27**:1, 1948.
4. Leiter, L.: The Role of Sodium Chloride in the Mechanism and Treatment of Congestive Heart Failure, Bull. New York Acad. Med. **24**:702, 1948.
5. Bradley, S. E., and Bradley, G. P.: The Effect of Increased Intra-abdominal Pressure on Renal Function in Man, J. Clin. Investigation **26**:1010, 1947.
6. Blake, W. D., Wegria, R., Keating, R. P., and Ward, H. P.: Effect of Increased Renal Pressure on Renal Function, Am. J. Physiol. **157**:1, 1949.
7. Berger, E. Y., Gladstone, M., and Horowitz, S. A.: The Effect of Anoxic Anoxia on the Human Kidney, J. Clin. Investigation **28**:648, 1949.
8. Futcher, P. H., and Schroeder, H. A.: Studies on Congestive Heart Failure: II. Impaired Renal Excretion of Sodium Chloride, Am. J. M. Sc. **204**:52, 1942.
9. Davies, C. E., and Kilpatrick, J. A.: Renal Circulation in Low Output and High Output Heart Failure, Clin. Sc. **10**:53, 1951.
10. Parrish, A. E.: The Bioassay of Adrenal Corticoids in the Urine of Patients With Congestive Heart Failure, J. Clin. Investigation **28**:45, 1949.
11. Deming, G. B., and Luetscher, J. A., Jr.: Bioassay of Desoxycorticosterone like Material in Urine, Proc. Soc. Exper. Biol. & Med. **73**:171, 1950.
12. Lasche, E. M., Perloff, W. H., and Durant, T. M.: Some Aspects of Adrenocortical Function in Cardiac Decompensation, Am. J. M. Sc. **222**:459, 1951.
13. Bornstein, J., and Trewhella, P.: Adrenocorticotropic Activity of Blood Plasma Extracts, Lancet **2**:678, 1950.
14. Dochios, M., and Dreifus, L. S.: Anticlimatic Hormone Studies in Patients Presenting Edema, Am. J. M. Sc. **222**:548, 1951.
15. Singer, B., and Venning, E. H.: Method of Assay of a Sodium-retaining Factor in Human Urine. Endocrinology. (In press.)
16. Conn, J. W.: Electrolyte Composition of Sweat, Arch. Int. Med. **83**:416, 1949.
17. Berger, E. Y., Quinn, G. P., and Homer, M. A.: Effect of Desoxycorticosterone on the Colon; Its Relation to the Action of Cation Exchange in Man, Proc. Soc. Exper. Biol. & Med. **76**:601, 1951.
18. Frawley, T. F., and Forsham, P. H.: Paper #59—33rd. Meeting of Association for the Study of Internal Secretions, June, 1951.
19. Merrill, A. J.: Mechanisms of Salt and Water Retention in Heart Failure, Am. J. Med. **6**:357, 1949.
20. White, A. G., Gordon, H., and Leiter, L.: Studies in Edema. II. The Effect of Congestive Heart Failure in Saliva Electrolyte Concentrations, J. Clin. Investigation **29**:1445, 1950.
21. Berger, E. Y., and Steele, J. M.: Electrolyte and Water Metabolism. Physiologic Considerations, M. Clin. of North America, p. 829, May, 1952.
22. Reynolds, T.: Sweat Sodium Levels in Congestive Heart Failure, Proc. Soc. Exper. Biol. & Med. **79**:118, 1952.
23. Bercu, B. A., Rokcin, S. N., and Massie, E.: Antidiuretic Action of the Urine of Patients in Cardiac Failure, Circulation **2**:409, 1950.
24. Carballeira, A., Elrick, H., Mackenzie, K. R., and Browne, J. S. L.: Effects of Single Intravenous Injections of Pituitary Growth Hormone to Normal Adult Humans, Proc. Soc. Exper. Biol. & Med. **81**:15, 1952.
25. Epstein, F. H., Leiser, G. T., and Berger, E. Y.: Renal Function in Decompensated Cirrhosis of the Liver, Proc. Soc. Exper. Biol. & Med. **75**:822, 1950.
26. Luetscher, J. A., Jr., and Deming, Q. B.: Treatment of Nephrosis With Cortisone, J. Clin. Investigation **29**:1576, 1950.
27. McCall, F., and Singer, B.: The Excretion of Chemically Determined Corticoids and a Salt-retaining Factor in Children With Nephrosis. (To be published.)
28. Bongiovanni, A. M., and Eisenmenger, W. J.: Adrenal Cortical Metabolism in Chronic Liver Disease, J. Clin. Endocrinol. **11**:152, 1951.

EFFECT OF EDEMA AND DIETARY SODIUM ON EFFICACY OF SODIUM REMOVAL BY CATION EXCHANGE RESIN

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IT HAS been stated that the magnitude of the uptake of sodium by cation exchange resin in the gastrointestinal tract of the edematous patient varies directly with the amount of dietary sodium.[1-4] This has been considered evidence that the sodium taken up is unabsorbed dietary sodium, rather than the sodium of gastrointestinal secretions.[2] In the present paper it is shown that the uptake of sodium by resin in a given edematous patient varies directly with the amount of edema present and is not affected by a change in dietary sodium until that change in sodium intake has caused an appreciable change in the extracellular fluid volume. The clinical significance of this is discussed.

CHEMICAL METHODS

The analytic methods employed for the determination of dietary sodium and potassium and fecal sodium and resin have been described previously.[5]

SUBJECTS

One 34-year-old normal man and two patients with congestive heart failure and edema were studied. The patients are described below.

W.S., a 56-year-old man, developed dyspnea and edema four years before the present admission. He was treated both as an outpatient and during numerous hospital admissions. The present admission was necessary because of the recurrence of edema. On examination dyspnea on slight exertion, venous distention, increased anteroposterior diameter of the chest, limited respiratory movement, pulmonary hyperresonance, prolonged expiration, a few sibilant râles, distant heart sounds, moderate hepatomegaly, and moderate edema were apparent. Blood pressure was normal. Teleoroentgenogram showed moderate cardiac enlargement. An electrocardiogram showed right axis deviation. Venous pressure was 21 cm. of water. Vital capacity was 2 liters. The results of hematologic studies and urinalysis were normal. The patient was thought to have pulmonary emphysema, cor pulmonale, and congestive heart failure.

W.L., a 62-year-old man, first noted edema and dyspnea five years before the present admission. He was treated both as an outpatient and during several hospital admissions prior to the present admission. The results of resin therapy in the treatment of this patient have been described previously.[5] Although resin was an effective therapeutic agent for this patient, dietary

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indiscretions led to a reaccumulation of edema. He was taken off resin several weeks prior to the present admission in order to permit his gastrointestinal tract to become free of resin. He was then admitted for the present study. On examination venous distention, a totally irregular cardiac rhythm, hepatomegaly, ascites, and severe edema were apparent. Blood pressure was normal. Teleoroentgenogram showed marked cardiac enlargement. Electrocardiogram showed auricular fibrillation and left axis deviation. The results of hematologic studies and urinalysis were normal. The patient was thought to have arteriosclerotic heart disease and congestive failure.

EXPERIMENTAL PROCEDURE

The two patients and the normal subject were studied by conventional metabolic balance procedures as previously described.[5]

The plan of study in each of the two patients was the same. The patient initially received a low sodium diet. Following a control period he ingested 120 meq. (approximately 15 Gm.) of a carboxylic cation exchange resin* three times daily. After the uptake of sodium by resin in the edematous patient on the low sodium diet had been determined, diuresis was accelerated by the administration of a mercurial diuretic and, in the case of W.L., by intravenous aminophylline and abdominal paracentesis. When the patient had become free of edema, these auxiliary measures were discontinued and the uptake of sodium by resin in the edema-free patient on a low sodium diet measured. The dietary intake of sodium was then increased and the uptake of sodium by resin in the edema-free patient on a high sodium diet determined. Each patient had taken digitalis daily for years and was continued on this medication throughout the study.

The normal subject received a high sodium diet during each of two five-day periods during which 360 meq. of resin per day were ingested. Throughout the second period 300 meq. of sodium per day were given by the administration of 2 liters of physiological saline intravenously.

RESULTS

The data from patients W.S. and W.L. are plotted in Figs. 1 and 2.† During the control period, in which a low sodium diet was given, each patient was in slightly positive sodium balance. There was no spontaneous diuresis.

After the control period the low sodium diet was continued and resin therapy was started. Each patient ingested 360 meq. of resin per day. The resin increased the fecal excretion of sodium to a quantity greater than that ingested, thus removing sodium from the body and initiating diuresis. During the first six days of resin therapy the uptake of sodium by resin was 26 per cent of the available exchange capacity‡ of the resin in the case of W.S. and 32 per cent of that ex-

*The preparation used was Resodec supplied through the courtesy of Mr. Edwin Boone of Smith, Kline & French Laboratories. Resodec contains a pharmaceutical grade of Amberlite IRC-50 in the ammonium and potassium forms. There are 58 meq. of potassium per 360 meq. of Resodec. Resodec was analyzed to determine the milliequivalents of resin per gram so that the exact dosage of 360 meq. daily could be weighed out for the patients.

†To simplify the presentation, days 10 through 16 and days 21 through 41 are omitted from the chart for W. L.

‡By per cent uptake of sodium by resin is meant the milliequivalents of sodium per 100 meq. of resin in the stool. The raw data for fecal sodium and resin were corrected for the fecal sodium and the fecal blank for resin as determined in the control period. In each case fecal sodium and the fecal blank for resin in the control period were 2 meq. and 1 meq., respectively.

change capacity in the case of W.L. Thus in each case there was a high uptake of sodium by resin while the patient was edematous, in spite of the fact that the dietary intake of sodium was low.

Throughout the rest of the period of treatment with resin and a low sodium diet the uptake of sodium by resin decreased as edema diminished. W.S. did not become free of symptoms until his extracellular fluid volume had returned to

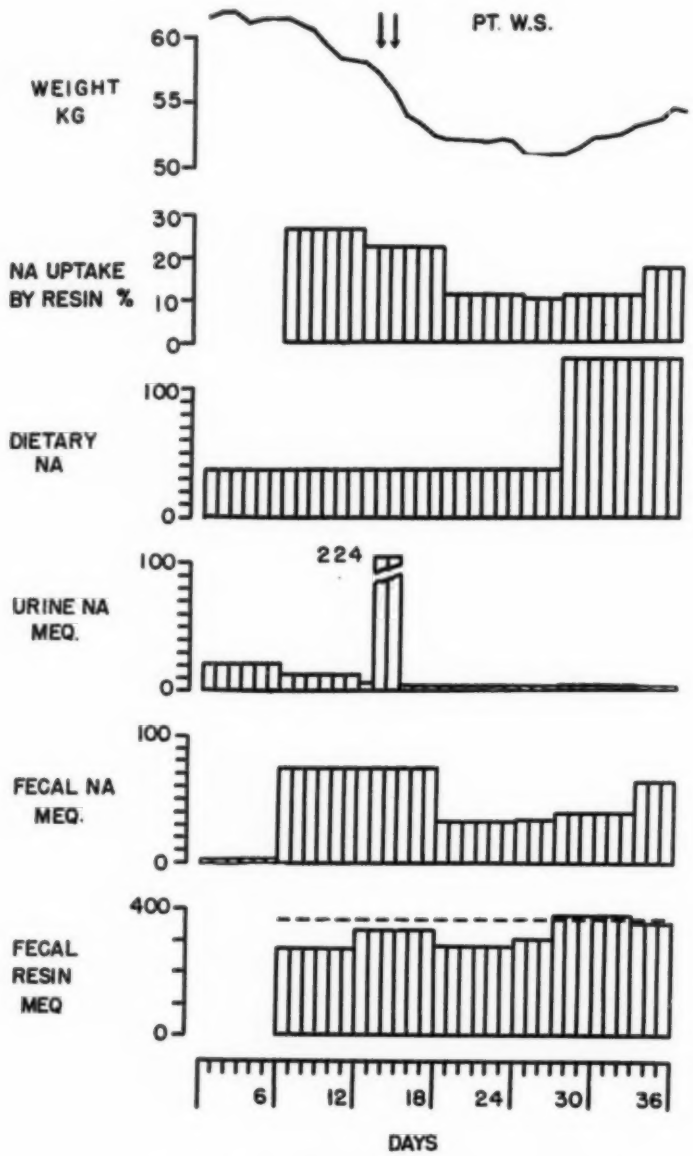

Fig. 1.—Results of study on patient W. S. The dosage of resin is indicated by the dotted line superimposed on the plot of fecal resin. The per cent uptake of sodium by resin is the milliequivalents of sodium per 100 meq. of resin in the feces. Each arrow above the weight curve indicates the administration of 2 ml. of sodium mercaptomerin intravenously.

normal. At that time the uptake of sodium by resin was only 11 per cent or 40 meq. per day. However, W.L. became symptom-free while mild edema was still present. He felt essentially well when his weight had fallen from 126 to 98 kg. At that time (during the four-day period of days 17 through 20) the uptake of sodium by resin was 22 per cent or 80 meq. per day.

After the patients had become free of edema but not dehydrated and while they were still on low sodium diets (in the case of W.S. during the nine-day period of days 19 through 27, and in the case of W.L. during the six-day period of days 42 through 47) the uptake of sodium by resin was 11 per cent in the case of W.S. and 10 per cent in the case of W.L.

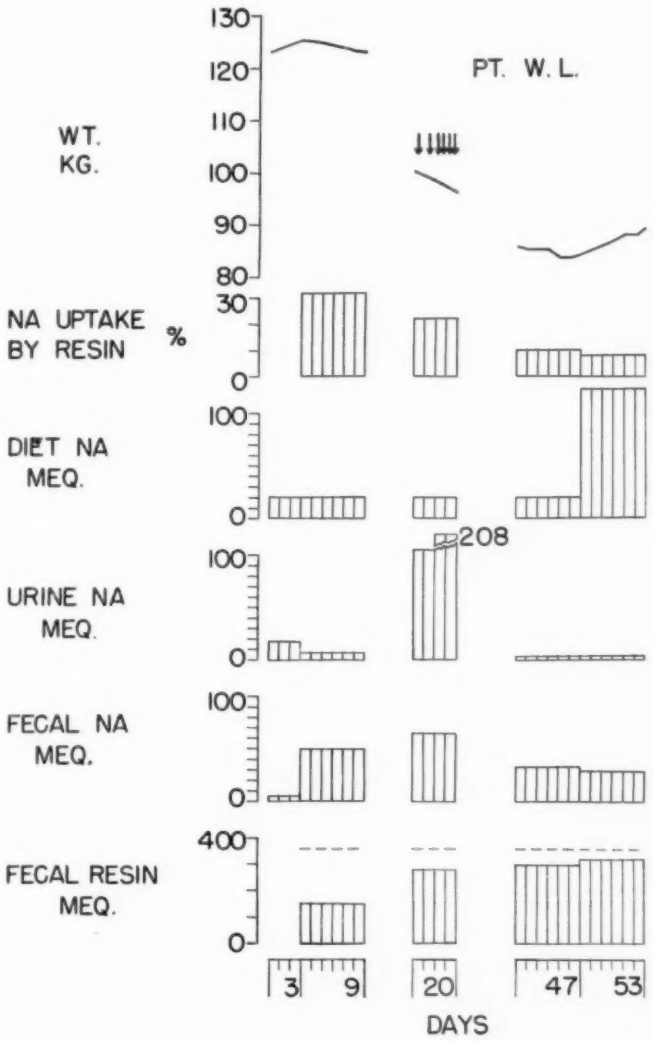

Fig. 2.—Results of study on patient W. L. Each arrow above the weight curve indicates the intravenous administration of 2 ml. of sodium mercaptomerin followed in two hours by 0.5 Gm. of aminophylline intravenously. For convenience in presentation, data from a number of days of the study are not plotted.

The dietary intake of sodium was then increased from 37 to 122 meq. in the case of W.S. and from 19 to 122 meq. in the case of W.L.* During the next six-day period the uptake of sodium by resin remained at 11 per cent in the case of W.S. and fell to 8 per cent in the case of W.L. During this same period each patient retained the increment in dietary sodium and gained edema as shown by the rise in weight. W.S. was studied for an additional three days during which his uptake of sodium by resin rose to 18 per cent. However, by this time he was again edematous and had regressed symptomatically. Thus each patient had a low uptake of sodium by resin while edema-free, in spite of the fact that the dietary intake of sodium was high.

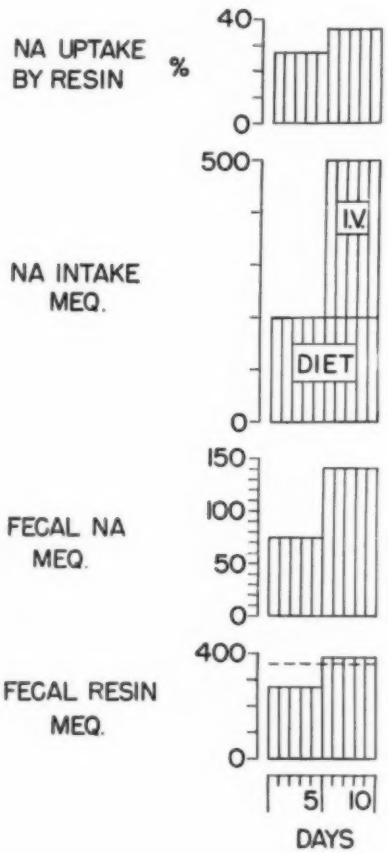

Fig. 3.—Results of study of the normal subject.

During sodium depletion the serum sodium concentration fell from 139 to 135 meq. per liter in the case of W.S. It rose to 141 meq. per liter with the subsequent high intake of sodium. There was no significant change in the serum sodium concentration in the case of W.L.

*The dietary intake of potassium changed at this time from 138 to 153 meq. per day for W. S. and from 151 to 167 meq. per day for W. L. These values include the potassium contributed by Resodec.

The data on the normal subject are plotted in Fig. 3. During the first five-day period the dietary sodium was 198 meq. per day* and the subject ingested 360 meq. of resin per day. The uptake of sodium by resin was 27 per cent. During the second five-day period the dietary intake of sodium remained at 198 meq. per day, and 300 meq. of sodium per day were given intravenously as physiologic saline. Three hundred and sixty milliequivalents of resin were ingested daily. The uptake of sodium by resin rose to 36 per cent. There was no sustained weight gain during the study. Thus in the normal subject, in contrast to the potentially edematous patient, an increased supply of sodium to the body resulted in an increase in sodium uptake by resin without a sustained expansion of extracellular fluid volume.

DISCUSSION

It is apparent from the data that in a given edematous patient the uptake of sodium by resin varies directly with the volume of the extracellular fluid. Furthermore, in the patient rendered free of edema in whom the uptake of sodium by resin has fallen to a low value, increasing the dietary sodium does not increase the uptake of sodium by resin until an appreciable quantity of edema fluid has reaccumulated. This indicates that sodium uptake by resin is not determined by exchange with dietary sodium before it is absorbed but rather that there is a physiologically regulated partition of sodium between resin and body.

In the normal individual the uptake of sodium by resin is increased by parenteral administration of saline in a quantity insufficient to cause a sustained increase in extracellular fluid.

In both the normal individual and the patient who becomes edematous when given sodium, it is probable that an important factor in the uptake of sodium by resin is the degree of activity of the sodium transport system of the intestine. The activity of this transport system in isolated loops of intestine has been shown to be increased by adrenocortical hormone.[6] Desoxycorticosterone acetate has been shown to decrease the uptake of sodium by resin.[7] One may postulate that with an increased amount of sodium in the body, adrenocortical activity is decreased, the sodium transport system of the intestine becomes less active, and more sodium is taken up by resin. This occurs in the normal subject without a sustained alteration in the extracellular fluid volume, but it occurs in the edematous or potentially edematous patient only when relatively large changes in extracellular fluid volume have been produced.

In both of the patients studied, resin was a valuable therapeutic agent when edema was present. When W.S. was free of edema, resin was relatively ineffectual in preventing the reaccumulation of edema on a higher sodium intake since the uptake of sodium by resin was only 11 per cent or 40 meq. per day. Higher uptake could be obtained in this patient only when the quantity of edema was sufficient to produce symptoms. In the case of W.L., in whom mild edema produced no symptoms, resin was a valuable agent in preventing the accumulation of more edema since with mild, asymptomatic edema present the uptake of sodium by resin was 22 per cent or 80 meq. of sodium per day.

*Dietary potassium intake in this and the subsequent period was 136 meq. per day.

CONCLUSIONS

1. In a given edematous patient the efficacy of orally administered cation exchange resin in removing sodium in the feces varies directly with the quantity of edema present.

2. In edematous or potentially edematous patients, increasing dietary sodium does not increase the efficacy of the resin until the quantity of edema has been appreciably increased.

3. Resin may be effective in removing body sodium from the edematous patient and yet relatively ineffective in preventing its reaccumulation on a higher sodium intake if the patient cannot tolerate the increase in extracellular fluid volume that occurs before the efficacy of the resin increases. If the patient can tolerate this increase in extracellular fluid volume without symptoms, resin is a valuable agent in preventing further increase in edema.

The dietetic aid of Mrs. Katherine S. Elliott and the nursing supervision of the patients by Miss Mary Rogers are very gratefully acknowledged.

REFERENCES

1. Danowski, R. S., Greenman, L., Peters, J. H., Mateer, F. M., Wergand, F. A., and Tarail R.: The Use of Cation Exchange Resins in Clinical Situations, Ann. Int. Med. **35**:529, 1951.
2. Dock, W., and Frank, N. R.: Cation Exchangers: Their Use and Hazards as Aids in Managing Edema, AM. HEART J. **40**:1, 1950.
3. Emerson, K., Jr., Kahn, S. S., and Vester, J. M.: Oral Use of Cation Exchange Resins in Treatment of Edema, Arch. Int. Med. **88**:605, 1951.
4. Mateer, F. M., Erhard, L. H., Price, M., Wergand, F. A., Peters, J. H., Danowski, T. S., Tarail, R., and Greenman, L.: Sodium Restriction and Cation Exchange Resin Therapy in Nephrotic Children, J. Clin. Investigation **30**:1018, 1951.
5. Duncan, L. E., Jr.: The Treatment of Edema by Removal of Body Sodium on a Cation Exchange Resin, Am. J. Med. To be published.
6. Dennis, C., and Wood, E. H.: Intestinal Absorption in Adrenalectomized Dog, Am. J. Physiol. **129**:182, 1940.
7. Berger, E. Y., Quinn, G. P., and Homer, M. A.: Effect of Desoxycorticosterone on the Colon: Its Relation to the Action of Cation Exchange Resins in Man, Proc. Soc. Exper. Biol. & Med. **76**:601, 1951.

THE DETERMINATION OF THE OXYGENATION OF BLOOD IN VITRO BY USING REFLECTED LIGHT

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LEYDEN, HOLLAND

A NEW method has been published by Brinkman and Zijlstra[1] to determine the percentage oxygen saturation of blood samples. Their starting point was that the intensity of light reflected by blood is dependent on the degree of oxygenation.

This method is worth paying attention to, for it has some advantages over the usual colorimetric methods (among others published by Brinkman and Wildschut,[2] Brinkman and Jonxis[3]), with which use is made of transmitted light. These advantages are: (1) The blood is not hemolyzed. Hemolyzation is necessary using the colorimetric methods with exception of the technique developed by Wood and associates.[4] (2) The intensity of the reflected light is independent of the quantity of hemoglobin, provided the blood layer, by which the light is reflected, is thick enough. It is, therefore, not necessary to estimate the hemoglobin content of the blood, as long as the percentage oxygen saturation is all the information required.

It is hardly necessary to state that the reflection method has some advantage over the gasometric method of Van Slyke and Neill[6] as over the colorimetric methods, such as the time required for a determination is short and, moreover, only small amounts of blood are needed. Therefore, it is possible to analyze many samples during a cardiac catheterization. In our opinion this is an important point in view of the incomplete mixing of the blood in the right side of the heart and even in the pulmonary artery, particularly in cases of left-to-right shunt.

Zijlstra[5] submitted the reflection method to a critical examination. It transpires from his discussion that the development of this method has been established in an empirical way and so far lacks a satisfactory theoretical foundation. We have felt satisfied with the Brinkman method for three years, but we think that a theoretical approach, which will be given here, might prove useful.

To that end the method by Brinkman will be described briefly, section A, the reflection theory will be discussed as far as necessary, section B, and the theory will be applied to the problem posed, section C. An explanation will be sought for the difference between the method found in an empirical way and the method which is theoretically right, section D. The direction for the determination as

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follows from the theory will be given, section E. Lastly comparative measurements with the method by Van Slyke, as these are determined by clinical applications, will be discussed, section F.

A. In the "haemoreflector"* (the name, adopted by Brinkman for his instrument) an incandescent lamp is present, the light of which falls via a red filter through a hole in a photo-elective cell on the bottom of a cylindrical cuvette, the measuring cuvette (Fig. 1). The sensitive side of the cell is directed towards the cuvette. The current delivered by the cell is measured by a galvanometer.

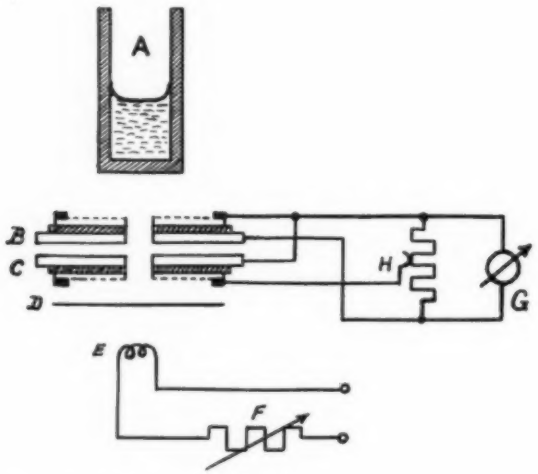

Fig. 1.—"Haemoreflector" of Brinkman.
A = cuvette; *B* = measuring cell; *C* = compensating cell; *D* = Ilfort 281 red filter; *E* = incandescent lamp; *F* = variable resistance; *G* = galvanometer; *H* = variable potentiometer.

Besides the blood in the cuvette reflecting the light, there is also reflection via the bottom of the cuvette. This reflection is not important for the measurement, therefore may be eliminated. To that purpose the light of the lamp falls directly on a second photoelectric cell, the current of which is sent in an opposite direction through the galvanometer. This current can be regulated by a potentiometer. The potentiometer is adjusted by putting an identical cuvette, filled with India ink in the "haemoreflector." It is assumed, that no light is reflected by India ink, so the measured light proceeds only from the bottom of the cuvette. By the potentiometer the deflection of the galvanometer is reduced to zero.

The sensivity is adjusted by a cuvette filled with a powder of a suitable red pigment. By varying the lamp current, the light spot of the galvanometer is by means of this adjusted on to a special place.

Without accession of the air, the blood sample is diluted one to one by a solution, (the dilution solution) containing 2 per cent NaCl, 0.3 per cent Na salicylate and 0.05 per cent NaCN. After mixing, this is put in the measuring cuvette and the galvanometer deflection determined. The degree of oxygenation is found by seeking the obtained value on a gauging graph.

*Constructed by the Kipp and Sons Company, Delft, Holland.

The gauging graph is obtained by the determination of two points:

1. A small quantity of blood is oxygenated for 100 per cent in a tonometer and the reflection in the "haemoreflector" determined in the way just now described.

2. A second quantity of blood is mixed one to one by a reduction solution containing 1 per cent $Na_2S_2O_4$, 2 per cent $Na_2B_4O_7$ and 0.3 per cent Na salicylate. The result is a mixture, the percentage oxygen saturation of which is 0 per cent. The reflection of this is also determined.

The gauging graph follows from both figures by plotting log u (u = galvanometer deflection) against the percentage oxygen saturation and by connecting the two points by a straight line.

This gauging line was chosen because it was thought that the following relation exists between reflection and oxygenation:

$$R_\infty = c\, e^{c_1 a} \quad \ldots\ldots\ldots\ldots\ldots\ldots 1$$

where $R_\infty = \frac{I_r}{I_o}$ = the reflection coefficient of an infinitely thick layer.

I_o = intensity of the exposing light.

I_r = intensity of the reflected light.

a = absorption coefficient, which is directly proportional to the oxygenation degree.

c and c_1 are constants.

Zijlstra himself unsettles this opinion, for he shows that the intensity of the reflected light depends for a great deal on the osmotic value of the dilution liquid. Enlargement of the osmotic value causes an increase of intensity. He rightly concludes that the dilution solution and the reduction solution must be isotonic. In reality, however, the reduction solution mentioned is strongly hypotonic with respect to the dilution liquid. The lowering of the freezing point of the first is 0.75° C* and of the second one 1.31° C*. Finally Zijlstra says that the compositions of the solutions are chosen in such a way that the values obtained by the gauging line just described are as much as possible in accordance with the values determined by the method of Van Slyke in the same time.

B. The radiation theory by Schuster[7] for scattering and absorbing media has been tested by many investigators in connection with different problems. Among them may be mentioned especially Dreosti,[8] who has in a fine mathematical way given an extension of this theory and has made his experiments with media, that are essentially equivalent with blood. He used mastix suspensions, the size of the particles of which he could vary and also the number of the particles. Moreover it was possible to color the mastix. The tests proved to confirm the formulas derived. Therefore it is justified to apply the theory mentioned to the problem of the "haemoreflector."

Three reflections appear in a cuvette filled with a scattering medium.

1. Against the bottom of the cuvette. This can be eliminated simply.
2. In the medium. This is the reflection in question at the "haemoreflector."
3. Against the limit layer between medium and air.

*We thank Prof. Dr. E. Havinga of the Organic Chemistry Department of the Leyden University for his willingness to measure the lowering of the freezing point.

The intensity of this last reflection depends on the thickness of the layer of the medium, the concentration of the scattering particles, the absorption coefficient and the scattering coefficient. If the product of the thickness of the layer and the concentration exceeds a certain amount at a given absorption and scattering coefficient this reflection will be zero. It is just as if the reflection appears in an infinitely thick layer. So by the "haemoreflector" the deflection of the galvanometer will be independent of the number of erythrocytes, provided, however, that the thickness of the layer in the cuvette is big enough.

For this case Dreosti gives the following equation:

$$R_\infty = p - \sqrt{p^2 - 1} \quad \ldots\ldots\ldots\ldots\ldots\ldots 2$$

in which is $p = \frac{a}{\beta s} + 1$

a = absorption coefficient
s = scattering coefficient
β = the backward scattered fraction of the total scattered light.

β is dependent on the bigness of the scattering particles. The fraction scattered back becomes bigger as the particles become smaller. This makes it clear, that the intensity of the reflected light depends on the osmotic value of the dilution solution, for smaller particles will originate at a bigger osmotic value, so that the galvanometer deflection will be bigger.

C. Equation 2 is not suitable to come to a simple gauging with the clinical use of the "haemoreflector." Therefore it is desirable to write down the equation in another form and to see if a justified approximation, which leads to a simple gauging, is possible.

Progression development proves to be a solution for the proposed purpose.

$$R_\infty = p\left\{1 - \left(1 - \frac{1}{p^2}\right)^{(\frac{1}{2})}\right\}$$

$$R_\infty = p\left\{1 - \left(1 - \frac{1}{2p^2} - \frac{1}{8p^4} - \frac{1}{16p^6} - \ldots\ldots\right)\right\}$$

$$R_\infty = \frac{1}{2p} + \frac{1}{8p^3} + \frac{1}{16p^5} + \ldots\ldots\ldots\ldots\ldots\ldots 3$$

At which term the progression of Equation 3 may be stopped, so that a good approximation will come into existence, depends on the magnitude of p and the accuracy desired. If a and βs might be determined separately an answer might be given at once. However in a simple way these magnitudes are not to be measured; therefore a reasoning of probabilities will be held and the result will be examined experimentally.

The "haemoreflector," from which a description will follow below, used by this examination, works on a wave length of about 700 mμ. The absorption coefficient of hemoglobin on this wave length is about 5 times as great as that of oxyhemoglobin. The deflection of the galvanometer in the first case is about 3.5

times smaller than in the second case. The graph of R_∞ against p (Fig. 2), in which also the equivalent values of $\frac{a}{\beta s}$ are set out on the abscissa, follows, that R_∞ varies a factor 3.5, when $\frac{a}{\beta s}$ changes from 2 to 10 (see in Fig. 2 the part between the dotted lines). That is $\frac{a}{\beta s} > 1$ so $p > 2$. In this case, the progression of Equation 3 may be broken off after the first term. So one gets:

$$R_\infty = \frac{1}{2p} \quad \ldots\ldots\ldots\ldots\ldots\ldots 4$$

To get an impression of the error in this approximation, one should look at the values for R_∞, when for p the value 2 is substituted in the Equations 2 and 4. The use of Equation 4 then proves to give an error of 8 per cent. As probably p is bigger than 2, the error will as a rule be smaller. For clinical application this error is certainly admissible.

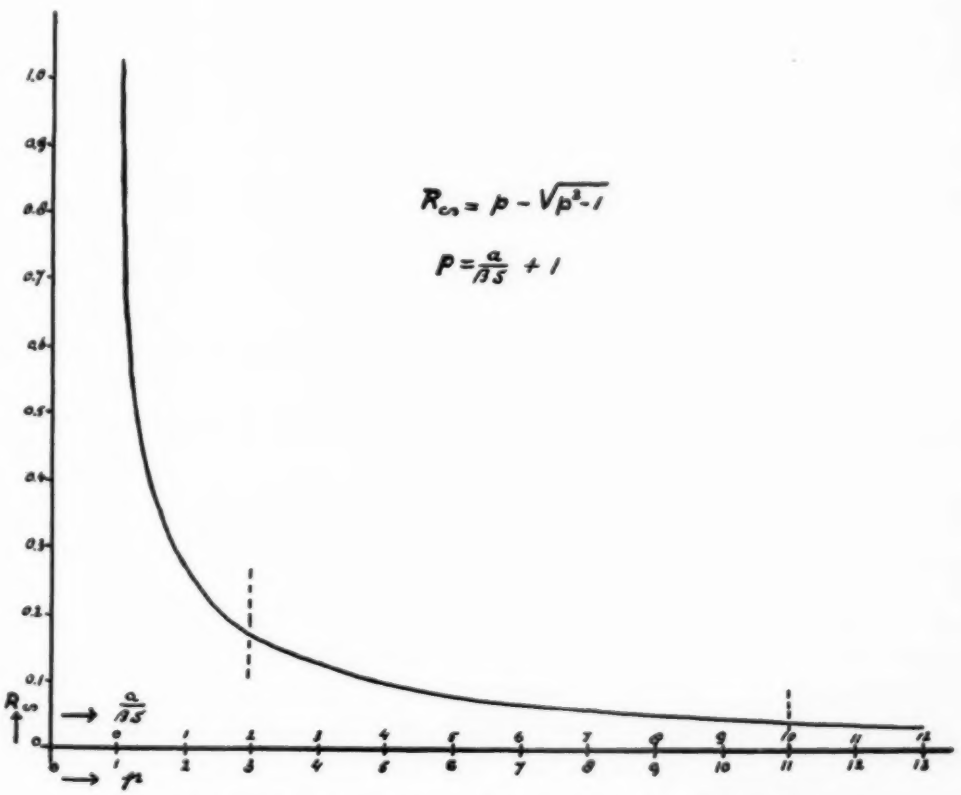

Fig. 2.—Graph of the reflection coefficient as follows from Equation 2.

The gauging line belonging to Equation 4 is a straight line, if the reverse of the galvanometer deflection is plotted against the percentage oxygen saturation, for R_∞ is directly proportional to the deflection of the galvanometer and p is directly proportional to the oxygenation degree.

In a slightly different way Amy[9] came to Equation 4. As a condition he stated that $a^2 > (\beta s)^2$ must be.

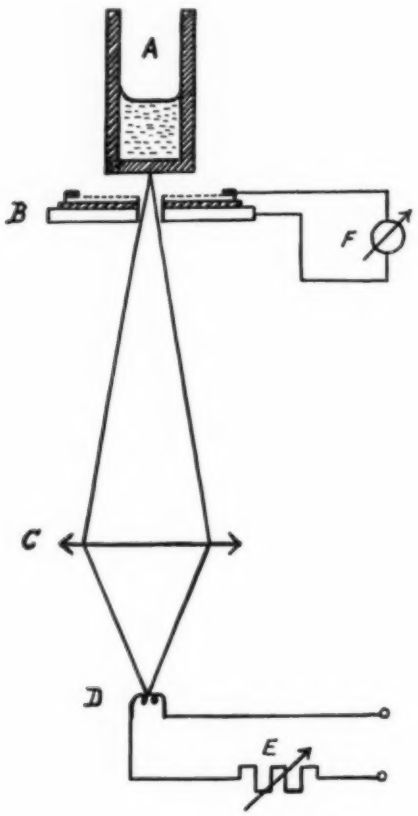

Fig. 3.—Modified "haemoreflector": *A* = cuvette; *B* = measuring cell; *C* = lens; *D* = incandescent lamp; *E* = variable resistance; *F* = galvanometer.

The control of the above conclusions is made by finding if the gauging line mentioned comes into existence by measuring samples with known relative degrees of oxygenation.

The present "haemoreflector" differs from the "Brinkman haemoreflector" in one point, namely in the way to eliminate reflection against the bottom of the measuring cuvette. The filament of the incandescent lamp is focussed by means of a lens on the bottom of the cuvette (Fig. 3). As the reflection is of the same kind as in a mirror this reflected light will return the same way, so it will not reach the photoelectric cell and a compensation cell is not necessary. An advantage of this is, that the cuvettes used do not need to be completely identical. A second advantage will be mentioned under section D.

Human venous blood *a* was taken during compression of a vein. Part of *a* was completely oxygenated *b*. The reflections of *a* and *b* were determined. By mixing *a* and *b* in known proportions, samples came into existence, the oxygenation of which in relative measure was known. For instance by mixing one to one an oxygenation degree comes into existence, which was exactly in the middle of those of *a* and *b*. The reflections were also determined of these mixtures. The reversions of the galvanometer deflections obtained were then plotted against the relative degree of oxygenation. It appeared that a linear relationship came into existence (Fig. 4).

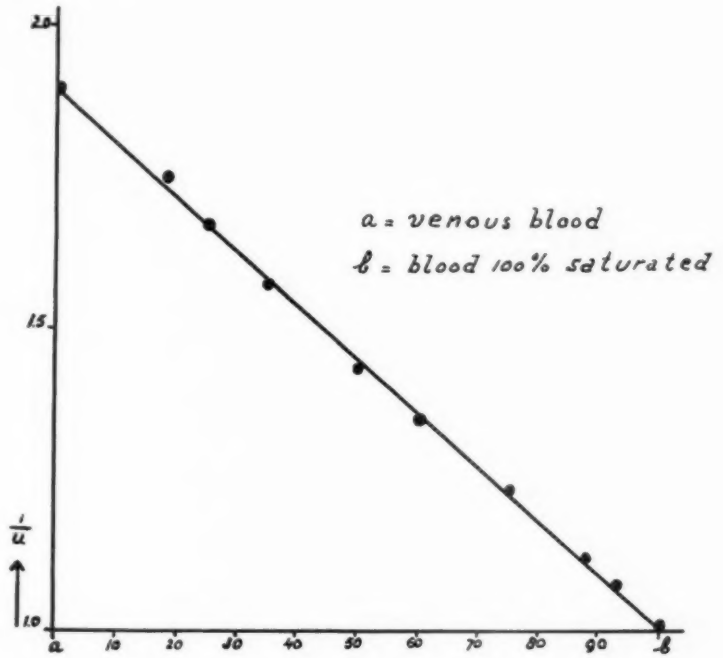

Fig. 4.—Checking graph of Equation 4.
The meaning of the abscissa scale is as follows:
10 is a mixture of 10 per cent *b* with 90 per cent *a*.
20 is a mixture of 20 per cent *b* with 80 per cent *a*.

So the reasoning of probabilities is correct and Equation 4 is applicable to the "haemoreflector."

D. The gauging line, suggested by Brinkman and Zijlstra is not right as is proved under section C. Compared with the method by Van Slyke, there is yet a good agreement. This is proved by Zijlstra. How can this apparent contradiction be explained?

When the strength of current delivered by a photo-electric cell is plotted against the intensity of the light falling upon it, a curve is obtained as drawn in Fig. 5. The initial part of it is nearly straight, but at larger intensities a curvature proceeds by the fact that the cell current increases less than the light intensity. This curvature is dependent on the resistance on which the cell is connected.

Little light falls upon the cell of the "haemoreflector" as described under section C, for the light reflected against the bottom of the cuvette does not reach the cell. Moreover the resistance of the galvanometer in use is small (about 50 Ohm). So the currents delivered by the cell are lying within the straight part of Fig. 5; and this is the second advantage of this construction.

When using the "Brinkman haemoreflector" however, the light reflected against the bottom is measured with the rest, so that the intensity of the light on the cell is much greater. The variations of the current caused by variation in the percentage oxygen saturation of the blood are consequently lying between the dotted lines in Fig. 5.

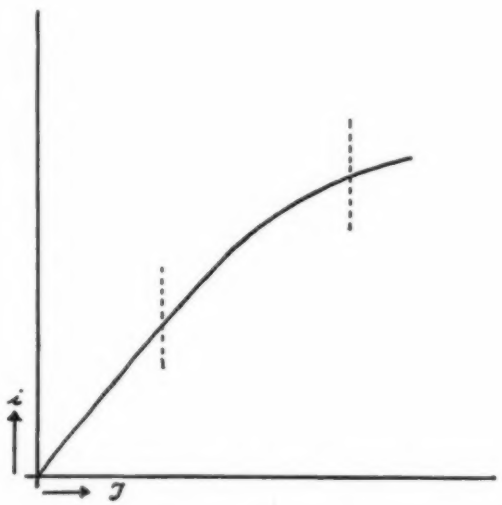

Fig. 5.—Cell current *i* against intensity of exposing light *I*.

If logarithm u (u = galvanometer deflection) is plotted against the percentage oxygen saturation as follows from Equation 4, curve 1 of Fig. 6 comes into existence. If, however, the current of the cell is not directly proportional to the intensity of the light falling on the cell (curved part of Fig. 5), then curve 1 will change into curve 2. From the nature of the case this latter curve will at low oxygenation nearly coincide with curve 1, while at high oxygenation the greatest difference will appear.

The last part of curve 2 is nearly straight. Now by drawing a gauging line, which coincides with the straight part of curve 2 it is possible to make determinations which are in accordance with values obtained by the method of Van Slyke, if the oxygenation degree does not become too low. This is obtained by making the reduction liquid strongly hypotonic, for in this way the point is almost obtained, where the straight part of curve 2 after lengthening cuts the logarithm u = axis (the straight line 3 of Fig. 6).

The incorrect assumption of Equation 1, on the one hand, the hypotonic reduction solution, and the use of the nonlinear part of the photoelectric cell

curve, on the other hand, compensate each other throughout a certain range of oxygenation percentages. The size of this range is dependent on the quality of the cell and the resistance on which the cell is connected. With a good compensation this range covers the saturation values from 55 to 100 per cent. The range is enlarged, if the compensation is diminished, but the values determined in the middle part of it will then be a little too small. With a range from 40 to 100 per cent saturation, the largest deviation, which occurs close to 70 per cent saturation, amounts to one or two per cent. In view of the standard deviation of one per cent (see under section F) this error does not seem to be important.

E. For a correct determination throughout the whole range from 0 per cent to 100 per cent saturation of the blood a "haemoreflector" as described under section C should be used (Fig. 3). As a filter may be recommended an interference filter with a wave length of 650 mμ may be used because at this wave length the difference between the absorption coefficient of oxyhemoglobin and that of hemoglobin is the greatest.

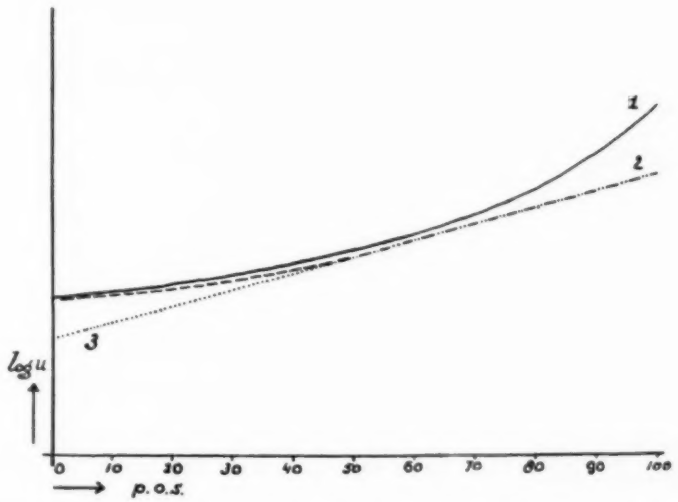

Fig. 6.—The logarithm of the valvanometer deflection against the percentage oxygenation saturation (P.O.S.). *1* Theoretical curve as follows from Equation 4. *2* The same, when the cell current is not directly proportional to the light intensity (part between the dotted lines in Fig. 5). *3* Gauging graph of the "Brinkman haemoreflector."

As a dilution solution, that recommended by Brinkman and Zijlstra may be used. The reduction solution, however, must have the following composition: 2 per cent $Na_2S_2O_4$, 2 per cent $Na_2B_4O_7$ and 0.3 per cent Na-salicylate. The lowering of the freezing point of this solution is 1.22° C., therefore nearly isotonic with the dilution solution.

As there is no compensating cell the cuvette with India ink is disposed of. The sensitivity is adjusted in the same way as with the "Brinkman haemoreflector."

In order to make the gauging line, the deflection of the galvanometer is determined by blood 100 per cent saturated (u_{100}) and the deflection by blood 0 per

cent saturated (u_0). The reversals of these values might be plotted now, but to obtain numbers, which are more suitable for practical use, these reversals are multiplied by u_{100}. So the point for 100 per cent saturation is $\frac{u_{100}}{u_{100}} = 1$ and for 0 per cent saturation $\frac{u_{100}}{u_0}$. With the modified apparatus used for this investigation the last term equals about 3.5. Figure 7 shows such a gauging graph.

Though the gauging line from individual to individual does not as a rule change much, it is desirable to determine the gauging line again for each individual, so that a big change appearing accidentally will not be overlooked.

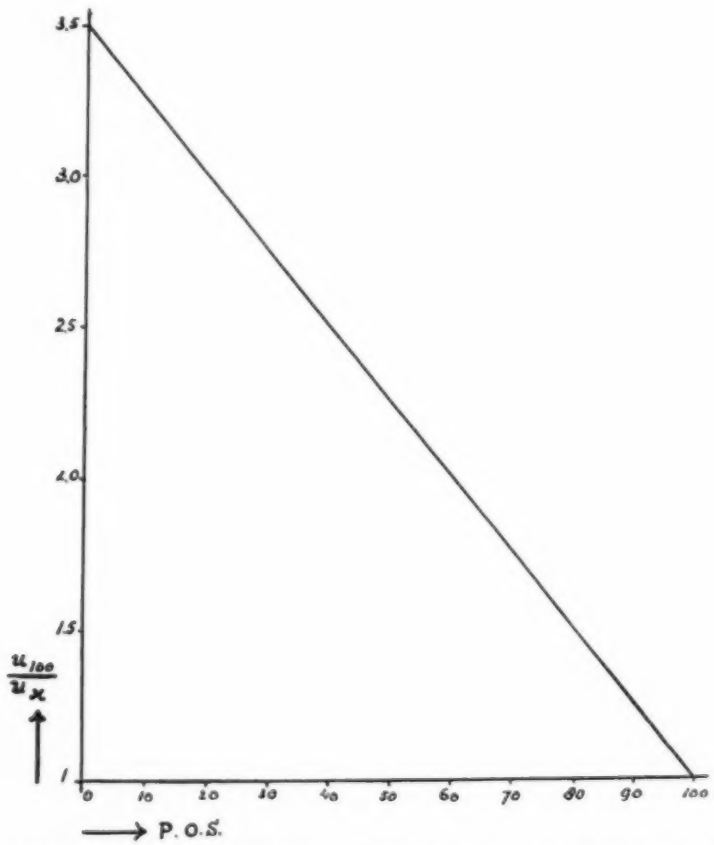

Fig. 7.—Gauging graph of the modified "haemoreflector." Percentage oxygen saturation (*P.O.S.*)

The galvanometer deflection of the blood sample is determined (u_x), the quotient $\frac{u_{100}}{u_x}$ made out and the oxygenation degree read out on the gauging graph.

Lastly it must be pointed out, that the method described is only possible, if no other pigments are present. The determination is disturbed by CO-hemoglobin, methemoglobin, and others.

F. Some comparative measurements have been made by means of, on the one hand, the method just mentioned and, on the other hand, by the method of Van Slyke.*

This comparison can be made in two ways: (a) With laboratory tests, in which both methods are always performed at the same time, and the oxygen capacity of each sample is determined by the method of Van Slyke. (b) With clinical routine determinations, as both methods are used in practice.

The last mentioned way although less accurate has been chosen. Beforehand, there must be checked which value may be attached to measurements of this kind.

1. When using both methods two different things are measured. With the gasometric method the total oxygen content of both plasma and erythrocytes is determined. With the "haemoreflector," however, only the oxygenation content of the erythrocytes is established.

In the calculation of the oxygen content from the results of the method of Van Slyke therefore the oxygen physically dissolved is taken into account. In this calculation the average values are used, which are determined for it. However, it will be clear, that this may cause a systematic error, which may be bigger than the casual error, as this latter follows from the duplicates.

2. It would be necessary with the method of Van Slyke to determine the oxygen capacity of each sample; however, this is not practical as the time per determination is too long. So the oxygen capacity of one sample of a series is estimated, and this also gives rise to a systematic error.

3. Because of the difference in time required by both methods the last samples of a series will be determined with the Van Slyke method much later than with the "haemoreflector." As the oxygenation degree of the blood decreases in the course of time, even if the samples are preserved on ice, the values determined by the Van Slyke method may sometimes be too low.

4. There is a possibility, that during the processes which the blood has to undergo for a determination, it may come in touch with air. The possibility is greater with the "haemoreflector" than with the Van Slyke method; therefore, the values of the reflector may be somewhat too high in some cases.

In the face of these four points, it will be clear, that a correct agreement can not be expected, but that the values will scatter, while the values determined with the "haemoreflector" will on the average lie a little higher than the values determined by the method of Van Slyke.

In Fig. 8 the results obtained are collected. On the abscissa the Van Slyke values are plotted and on the ordinate the values determined by means of the "haemoreflector."

The situation of the points is in accordance with the considerations discussed above.

The points marked with ⊙ are inserted to give an impression of the error, which may be made by the Van Slyke method, when the oxygen capacity of each sample is not determined. The case was that of a small child, the blood of whom was diluted by saline infusion during catheterization. Consequently the hemoglobin concentration of the last samples was less than that of the first. Using

*We owe thanks to Dr. Th. Strengers, who allowed these measurements to be executed in the "O. L. Gasthuis," Amsterdam; and to Miss M. v.d. Kolk, who made all the determinations.

the oxygen capacity of the first sample in the percentage oxygen saturation calculation of the last ones resulted in too low values.

The determination of the standard deviation from the above results is difficult, for the scattering of the points is due to both a systematic and a casual error (see the four points mentioned). If the error is only systematic, then the "haemoreflector" numbers are on the average 1.2 per cent in the percentage oxygen saturation scale higher than the numbers estimated with the Van Slyke method. If, however, the error is only casual, then the mean deviation per determination is 2.5 per cent saturation of the blood. The actual error will be less than this last one.

From the duplicates, which are made of each sample, it follows that the standard deviation of the "haemoreflector" readings amounts to one per cent difference in oxygen saturation.

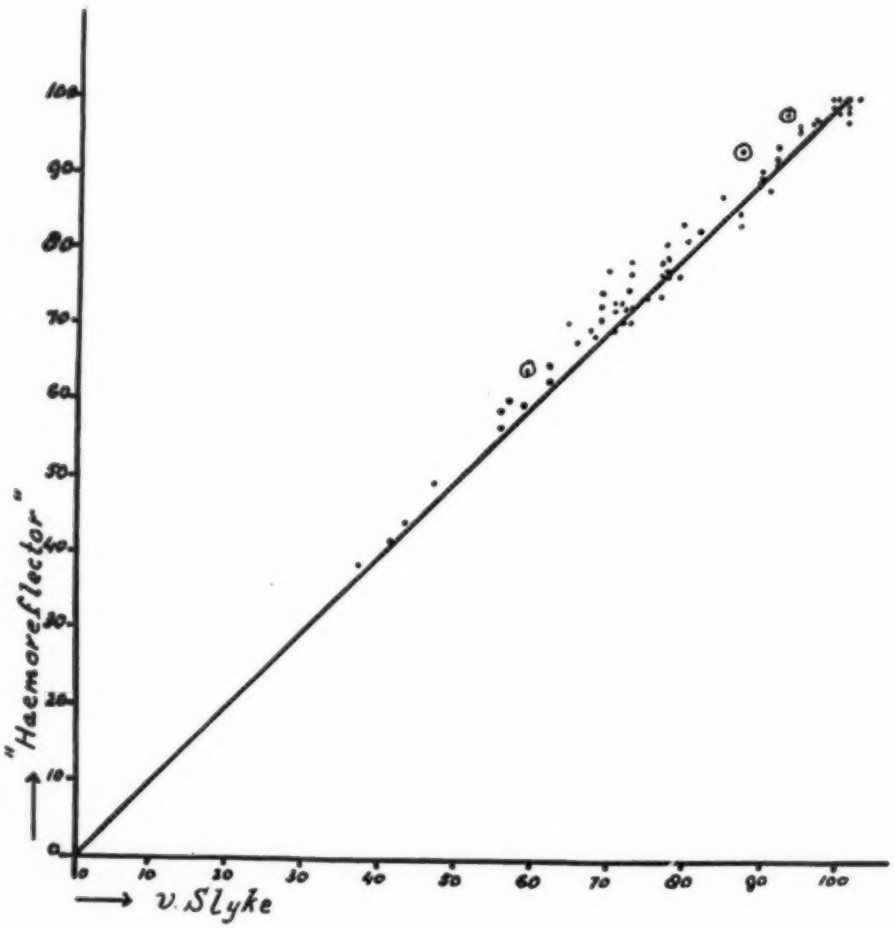

Fig. 8.—Results of the comparative measurements with the "haemoreflector" and the Van Slyke method.

CONCLUSION

The method of Brinkman and Zijlstra for determining the percentage oxygen saturation of blood samples gives reliable values, if the oxygenation degree is not too low. From the theory it follows, that some errors are made, which compensate each other over a range of the percentage oxygen saturation, which covers the values usually encountered, section D. If, however, the oxygenation degree falls below this range, the estimations err on the high side.

The modified "haemoreflector" section C and its use section E are in accordance with the theory. With this apparatus a correct determination of the saturation degree can be performed throughout the whole range from 0 to 100 per cent saturation of the blood, with a standard deviation of 1 per cent in the percentage oxygen saturation scale. The condition, however, is, that no other pigments as CO-hemoglobin, methemoglobin, and others are present.[1] Bearing in mind the last restriction, the advantages (short determination time, small amounts of blood, no hemolysis of the blood, no estimation of the hemoglobin contents) make the reflection method preferable to the gasometric method.

SUMMARY

A method published by Brinkman and Zijlstra is referred to, by which it is possible to determine the degree of oxygenation of blood samples in vitro. By this method the fact is used, that the color of the light reflected by the blood depends on the percentage oxygen saturation. The advantages of this method are mentioned. It was found desirable to investigate the theoretical basis.

One after another the following points are dealt with:

A. A short description is given of the "Brinkman haemoreflector" and the way it is used.

B. The reflection theory of Schuster, as it has been extended by Dreosti, is discussed so far as necessary for the purpose proposed.

C. The theory is applied to the "haemoreflector." An approximation formula (Equation 4) is derived and confirmed experimentally with a modified "haemoreflector."

D. The instruction for the use of the "Brinkman haemoreflector" is not in accordance with the theory discussed earlier. There is a good agreement, however, when compared with the method of Van Slyke. An explanation of this phenomenon is given. It is evident, that there is a range of the percentage oxygen saturation scale (from x to 100 per cent saturation, where x is dependent on the quality of the photo-electric cell and the resistance on which the cell is connected), where the apparatus gives reliable values. In practice, x is found to vary from 40 to 55 per cent.

E. The method which uses a modified "haemoreflector" and which is in accordance with the theory is described briefly. It allows a correct determination throughout the whole range from 0 to 100 per cent saturation of the blood.

F. The results of comparative measurements between the "haemoreflector" and the method according to Van Slyke are discussed. The agreement proves to

answer the expectations, as these may be formed on account of four considerations, which are worked out in some detail.

The standard deviation of the reflection method, as it follows from duplicate readings, is 1 per cent difference in oxygen saturation.

We are much indebted to Dr. H. A. Snellen for his helpful advice and criticism, and to Miss J. Seyl, and Mrs. E. Rodrigo-de Heer for their help in preparing the English text.

REFERENCES

1. Brinkman, R., and Zijlstra, W. G.: Determination and Continuous Registration of the Percentage Oxygen Saturation in Small Amounts of Blood, Arch. chir. neerl. **1**:177, 1949.
2. Brinkman, R., and Wildschut, A. J. H.: A clinical Method for Rapid and Accurate Determination of Oxygen Saturation in Small Amounts of Blood, Acta Med. Scandinav. **94**:459, 1938.
3. Brinkman, R., and Jonxis, J. H. P.: The Estimation of Arterial Unsaturation, Especially in Pediatric Conditions, Acta Med. Scandinav. **94**:453, 1938.
4. Wood, E. H., Geraci, J. E., and Groom, D. L.: Photoelectric Determination of Blood Oxygen Saturation in Man, Federation Proc. **7**:137, 1948.
5. Zijlstra, W. G.: Fundamentals and Applications of Clinical Oximetry, Thesis Groniagen, 1951.
6. Van Slyke, D. D., and Neill, J. M.: Determination of Gases in Blood and Other Solutions by Vacuum Extraction and Manometric Measurements, J. Biol. Chem. **61**:523, 1924.
7. Schuster, Sir A.: Radiation Through a Foggy Atmosphere, Astrophys. Journ. **21**:1, 1905.
8. Dreosti, G. M.: Absorpsie en verstrooiing van lig in melkglas, Thesis Utrecht, 1930.
9. Amy, L.: Sur le couleur des corps par reflection, I Etude théorique, Revue d'Optique Théor. et Instr. **16**:81, 1937.

TECHNIQUES FOR FACILITATING THE QUANTITATIVE ANALYSIS OF SPATIAL VECTORCARDIOGRAMS

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WILSON and associates[1] made a notable contribution to electrocardiography when they placed the important relationship between the QRS complex and the T wave on a more quantitative basis by promulgating the ventricular gradient concept. Unfortunately, the determination of the ventricular gradient from a conventional electrocardiogram is rather difficult because it entails measuring the area under irregular curves. Consequently, the method is not widely used clinically. Such difficulties appear superficially to be even worse when the analysis of spatial vectorcardiograms is contemplated because in this field one is dealing with such generally unfamiliar concepts as the temporal and the three three spatial dimensional distributions of complex curves. The purpose of the present report is to show that it is possible to analyze vectorcardiographic curves fairly easily and directly by making quantitative measurements of several of their salient features. By subjecting these measurements to simple mathematical treatment it is possible to extend the precision of several concepts developed by electrocardiography. In addition, possibilities for taking advantage of properties peculiar to vectorcardiograms are suggested, including the application of quantitative criteria which do not depend solely upon the disposition of the principal axes but also take into account other aspects of vectorcardiographic loop morphology.

Fairly accurate quantitiative measurements could be made directly from wire models of spatial vectorcardiograms, but since about two and one-half hours are required just to make a single model,[2] the method would not be clinically useful. Similarly, stereoscopic vectorcardiograms are difficult to record accurately and even more difficult to analyze. Certain techniques which make possible an easier approach to quantitative analysis are described here.

ILLUMINATED SCREEN COORDINATES

For the correct interpretation of a vectorcardiogram it is necessary to know the location of the isoelectric point rather precisely. As one watches the screen of an oscilloscope tube while a vectorcardiogram is being inscribed, it is usually

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quite easy to see where the isoelectric point lies because the luminous dot produced by the electron beam rests immobile during diastole. However, when one later looks at the finished photographic print of the same vectorcardiogram the isoelectric point is often no longer easy to find. Decreasing the halation of the tube screen and increasing its resolving power would both help to decrease the obscuring effects of crowding around the isoelectric area. Nevertheless, the difficulties in finding the isoelectric point resulting from superimposition of smoothly overlapping P, QRS, or T loops would remain. This problem can be readily solved by the use of screen coordinates.

When a sheet of plastic like E. I. DuPont's Lucite is illuminated from the edge any scratches on the surface will glow, while smoothly polished adjacent regions will not. If one places a sheet of appropriately scratched plastic in front of an oscilloscope screen, advantage may be taken of this property of internal reflection to provide bright coordinate markings without interfering with the dark background required for oscilloscope photography. Further, such luminous coordinates do not interfere with the vectorcardiographic pattern even when the two superimpose, since the coordinate markings can be made of much lower brightness than the cathode ray trace and tend to be further distinctive because of their constant shape and position. Some commercially available oscilloscopes are already provided with illuminated coordinate systems, such as the Model 512 oscilloscope put out by Tektronix, Inc., Portland, Oregon. If one plans to use an oscilloscope which is not so provided, the method illustrated in Fig. 1 may be adapted to any oscilloscope without dismantling or altering the instrument. The edge of the plastic which faces the filament of the incandescent lamp in the lightbox may be bent to shape easily after being dipped in boiling water. After one has scratched the desired type of coordinate markings to an approximate depth of 0.25 to 0.5 mm. into the surface of the plastic which faces the oscilloscope screen, these marks will glow against an almost completely dark background if the face of the tube has been shielded from extraneous light in the room. Some light scatter will occur from the free edges of the plastic, but this can be minimized by polishing the edges or can be completely eliminated by painting, taping, or otherwise masking them. With the rheostat placed in series with the incandescent lamp and the power supply, the brightness of the coordinates may be varied according to whatever photographic conditions are desired.

To make use of the coordinate system while taking a vectorcardiogram the operator determines the location of the isoelectric point visually during diastole. This isoelectric point dot may then be centered behind the luminous dot of the coordinate markings on the sheet of plastic (Fig. 2*A* and 2*B*) by appropriate adjustments of the vertical and horizontal centering controls of the oscilloscope. The vectorcardiogram is thereby brought into a constant frame of reference in which linear extensions of the vertical and horizontal markings will always intersect at the isoelectric point in the finished photographic print. These vertical and horizontal markings are not carried all the way down to the isoelectric dot on the plastic sheet because that might tend to clutter up this important and often crowded area and so confuse the interpretation of the vectorcardiogram. It is advisable that the coordinate system be constructed so that the coordinate mark-

ings may be moved and centered in different quadrants in front of the tube screen. This enables the operator to make use of the full size of the screen in the occasional case where the QRS loop of the vectorcardiogram is of high voltage or shows a large development in an unusual direction. Nevertheless, when electrode polarities are arranged according to Grishman and Scherlis,[3] there are few exceptions to the general rule that centering of the markings somewhat above and to the left of the center of the screen will suffice for all cases in all planes. The markings themselves were deliberately placed above and to the left of the isoelectric dot on the plastic sheet because this is the area which vectorcardiographic tracings least often enter extensively, regardless of the plane of the body being studied, when these same polarities are used.

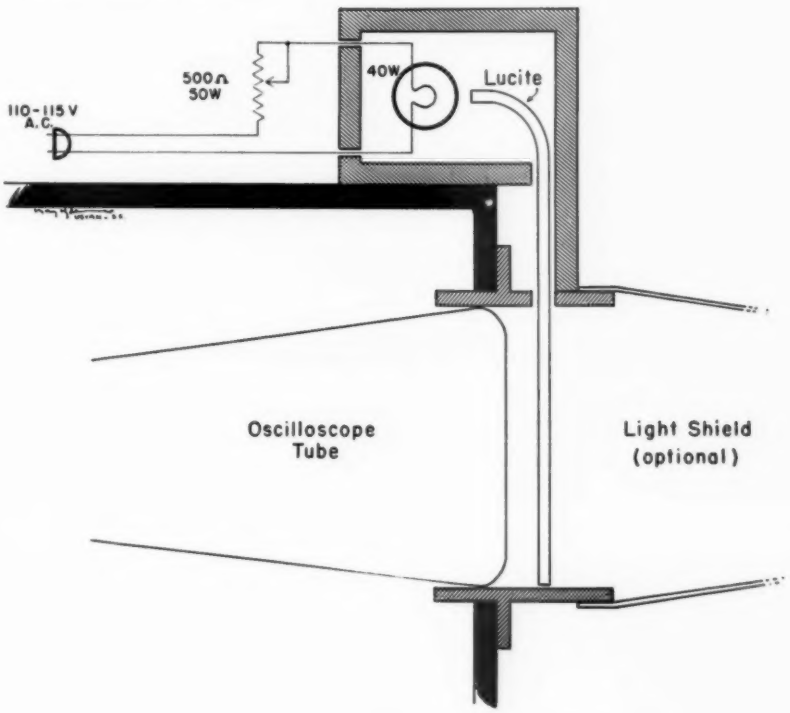
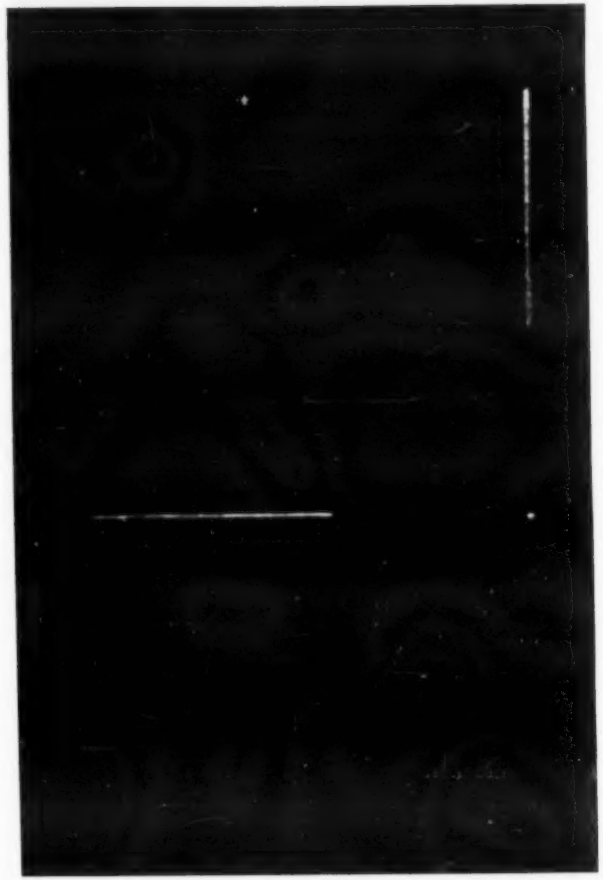


Fig. 1.—Illuminated coordinate apparatus.

In addition to locating the isoelectric point precisely, the asymmetrical position of the markings allows one to orient the vectorcardiogram immediately as to up and down, right and left. Further, the length of the lines serves as a linear standard for calibrating the amplifiers and for determining the scale of enlargement of the final photographic print of the vectorcardiogram.

DETERMINING SPATIAL COORDINATES AND ANGLES

The necessary quantitative vectorcardiographic measurements may be made quite easily if some sort of protractor and calibrated grid arrangement is used. The two mutually perpendicular coordinate lines described above may be used as



A.

Fig. 2A.—Coordinate markings described in the test.

B.

Fig. 2B.—A frontal plane vectorcardiogram centered on the coordinate markings.

guide marks for superimposing a transparent protractor-grid device on plane vectorcardiograms in correct alignment. A protractor-grid marking system which has been found to be quite satisfactory is shown in Fig. 3. The heavy grid markings may be conveniently placed one centimeter apart and the lighter markings at one-half centimeter intervals. This pattern may be marked in some bright color or colors on a sheet of fairly stiff and transparent material such as Cellophane or unexposed roentgenogram film that has been cleared in a fixative. The device may then be placed on a vectorcardiogram as an overlay in such a manner that the isoelectric point of the vectorcardiogram lies directly under the center of the overlay, that is, where the 0 to 180 degrees and the 90-degree axes of the

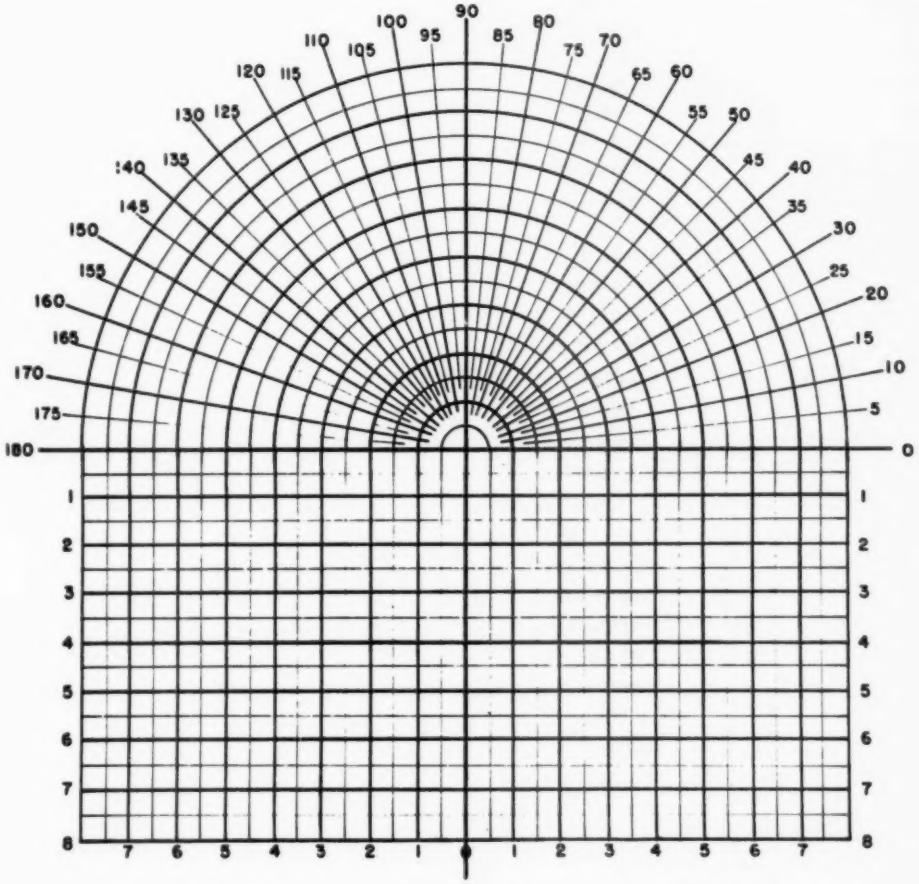


Fig. 3.—Protractor and calibrated grid pattern of the overlay.

protractor markings intersect. This will occur automatically if the 90-degree axis is lined up directly over the vertical coordinate marking on the vectorcardiogram and the 180-degree axis over the horizontal marking, for example. The device will then be correctly positioned to enable one to plot the radius vector and the vectorial angle of any given point on the vectorcardiogram. To plot such polar coordinates for any point below the 0 to 180 degree axis it will obviously be necessary to align the overlay in a similar fashion as above except upside down.

In practice the complete polar coordinate system for determining points in a plane has not been very helpful. However, the determination of just the vectorial angle alone is useful in several ways, and of course more or less similar measurements have been advocated many times in the past by electrocardiographers as well as vectorcardiographers. Formulations which are more rewarding than those depending on the measurement of vectorial angles alone may be made if one uses the calibrated grid part of the measuring device to determine the spatial coordinates of a point on a vectorcardiogram according to the principles of solid geometry. Any point on a plane surface may be determined by any two real numbers (x,y) plotted along the X and Y axes, respectively, of the familiar Cartesian coordinate reference system. In solid analytic geometry a third or Z axis is added at right angles to both of the previous two so that measurement a'ong the third spatial dimension is possible. Thus any point in space may be determined by the numbers (x, y, z) which are known as the rectangular coordinates of that point. After aligning the grid overlay on the vertical and horizontal vectorcardiogram coordinate markings as before, with the grid markings arranged above, below, to the right, or to the left, as necessary, one may determine the rectangular coordinates of any point on a vectorcardiogram. To obtain all three coordinates of a point on a spatial vectorcardiogram one may plot the up-and-down and the side-to-side values from the frontal plane projection, for example, and then derive the back-to-front value from the corresponding horizontal or sagittal plane vectorcardiogram.

In determining the three rectangular coordinates of a point on a spatial vectorcardiogram it is necessary to be sure that one is dealing with corresponding points on any two plane projections. Usually this may be done easily by simple inspection. When the cathode ray beam is interrupted periodically at a constant frequency as a timing signal,[4] segmented vectorcardiographic loops are produced in which each loop or any corresponding part of it contains the same number of timing segments in all three planes. Consequently, when there is doubt about the analogy between two particular points on different plane projections, one can count forward or backward the same number of segments along the corresponding loop in each plane from some more obviously equivalent points on each and so arrive at corresponding sites. It is unnecessary to record the three plane projections of a spatial vectorcardiogram simultaneously for the same reason which permits one to make a clinical interpretation from different heart beats in each of the various leads of a conventional electrocardiogram. Unless the subject is breathing deeply, is shifting his body position during the recording, or there are intermittent cardiac arrhythmias or other phasic disturbances, meaningful rectangular coordinates for any point on the curve may be determined without difficulty. The presence of disturbing factors is nearly always obvious to an alert operator during the recording of the tracing, at which time he can compensate for most of them.

A Cellophane overlay on which the axes of various electrocardiographic leads have been printed accompanies Grishman and Scherlis' recent book on vectorcardiography.[3] When used as intended, their overlay helps one to visualize the relation between an observed electrocardiographic complex and the vectorcardio-

graphic loop from which it was derived. The overlay is not adapted for making accurate quantitative vectorcardiographic measurements, however.

THE APPLICATION OF TRIGONOMETRY AND GEOMETRY

It is unfortunate that there is no unanimity of method for recording vectorcardiograms; nearly every author develops his own technique at present. It is, therefore, still premature to set up numerical standards which will delimit, as carefully as normal variation permits, the various vectorcardiographic entities which we study in the human patient. Nonetheless, it is hoped that the advantages inherent in this approach can be brought out in the following discussion. A standard technique for vectorcardiographic electrode placement will surely emerge sooner or later. The author believes that the "perfect cube" method[3] is the best adapted for mathematical analysis of any method hitherto described. Although it has some defects, it approaches the desirable objective of providing semidistant electrodes arranged equidistantly and orthogonally around the hypothetical electrical center of the heart. A vectorcardiogram recorded in this way may be considered to be inscribed in "unweighted space." As a result, a unit of potential difference theoretically has the same value when applied to any of the three primary dimensions of spatial vectorcardiography, solid geometry, or spherical trigonometry. This means that we may apply the formulas and theorems of the latter disciplines directly to the analysis of frontal, sagittal, or horizontal plane vectorcardiograms recorded by the cube technique without having to introduce troublesome correcting factors. However, since any system could be arbitrarily considered to represent "unweighted space" and because any system requires that one make assumptions about the electrical homogeneity of the body, which only approximate the true situation, all that is really needed is general agreement on one standard technique.

Electrocardiography has demonstrated that an unduly large or small displacement of the peak of the P, QRS, or T wave from the isoelectric line in certain leads may be clinically significant. So-called voltage criteria have thus been set up to help define (electrical) ventricular hypertrophy, for example. Some of these criteria depend on the findings in only a single lead or axis, as in the case where the upper limits of normal for adult QRS voltage in Lead aV_L are set at between 11 and 13 mm. of displacement of the peak of the R wave when the electrocardiograph is standardized for the usual sensitivity of one millivolt per centimeter. Others depend on the sum of the findings along two more or less perpendicular axes, such as the criterion which states that the arithmetic sum of the S wave in V_1 plus the R wave in V_5 should not exceed 35 mm. in normal adults.[5] This means that the length of the principal or long axis of the vectorcardiographic QRS loop is being estimated more or less according to its projection on the whole horizontal plane rather than just in one dimension. However, still greater precision is possible if we utilize the relations of solid geometry which will allow us to measure the actual length of the principal axis of the QRS loop in three dimensional space. This is the distance from the intersection, *O*, of the three coordinate planes to the extremity, *Q*, of the longest instantaneous QRS vector, represented in Fig. 4 by the line *OQ*.

In Fig. 4 (x, y, z) may be considered to be the rectangular coordinates of Q. Since they may also be considered to be the length (a), breadth (b), and depth (c) of the rectangular parallelepiped whose solid diagonal is OQ, the length of OQ may be easily determined by the simple Pythagorean relation:

$$OQ = \pm \sqrt{x^2 + y^2 + z^2} \qquad (1)$$

Similarly, the length of the principal axis of the T loop, OT, may be determined from the rectangular coordinates (x_1, y_1, z_1). The same determination may also be made for the P loop.

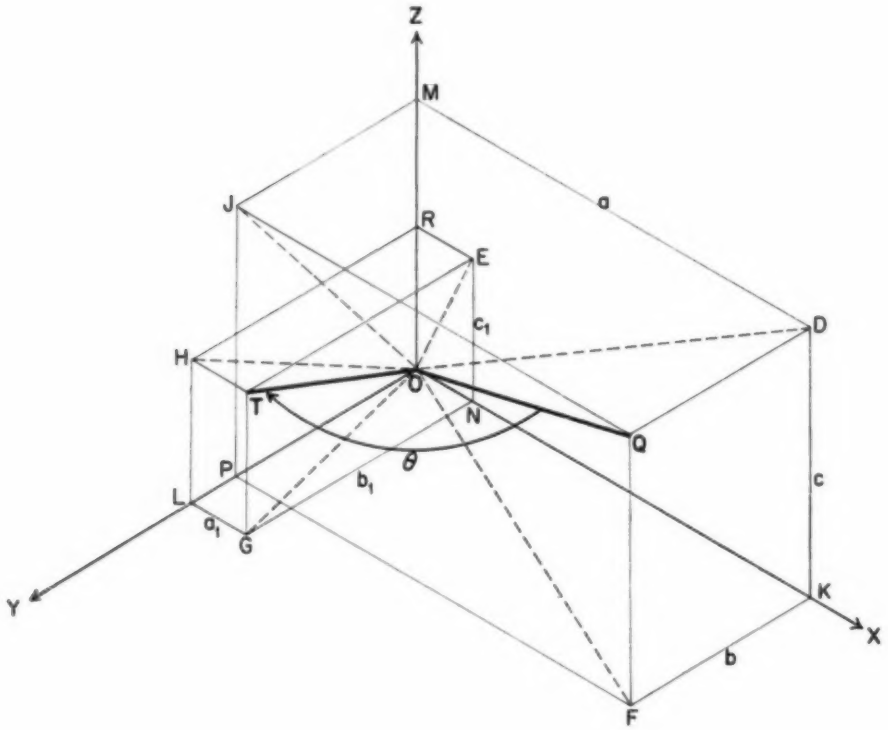


Fig. 4.

In scalar electrocardiography a T wave may be relatively low compared to the height of the R wave in the same lead for either or both of two reasons. The first is that the absolute magnitude of the T loop is small although its spatial orientation with respect to the QRS loop is normal, the second that the spatial angle between the principal axes of the QRS and T loops exceeds the normally rather small or absent divergence. A change in the electrical position of the heart may make the T wave appear to be rather low relative to what one expects empirically in a given lead although the relation between the QRS and T loops may remain within normal limits. Vectorcardiographically the differentiation between the two conditions or the determination of their coexistence is easy and

immediate when either condition is well marked. However, a greater precision is possible if one determines quantitatively not only the absolute spatial magnitude of the principal T axis but also the absolute value of the spatial angle between the principal QRS and T axes. This will throw the two variables into greater relief, making possible a more precise evaluation of the borderline case, although there will still be considerable overlapping of the ranges of the various clinical entities involved depending upon age, electrical position of the heart, biologic variation, and so forth.

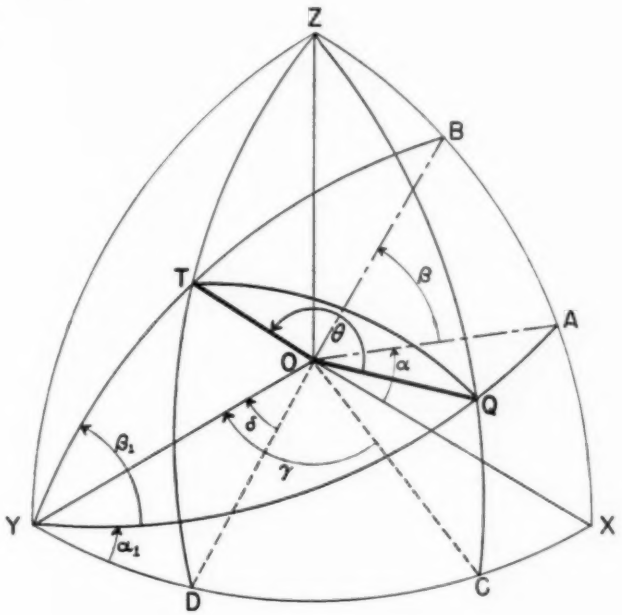


Fig. 5.

The value of the spatial angle between the principal axes of the QRS and T loops, indicated by θ in Fig. 4, may be readily calculated after one has determined the absolute magnitude of OQ and OT according to Equation (1). Solid analytic geometry gives us the equation for the angle between two lines which states that

$$\cos\ \theta = \frac{aa_1 + bb_1 + cc_1}{\sqrt{a^2 + b^2 + c^2}\quad\sqrt{a_1^2 + b_1^2 + c_1^2}} \qquad (2)$$

where (a, b, c) and (a_1, b_1, c_1) are the direction numbers or direction components of the lines.[6] Now our rectangular coordinates (x, y, z) and (x_1, y_1, z_1) are members of an infinitely large series of direction numbers which establish through the constancy of the relation between themselves the direction which a line takes in leaving the origin or isoelectric point. The only difference is that each set of rectangular coordinates uniquely determines a definite point on a directed line. Therefore, it is only necessary to substitute x for a, y for b, etc., in Equation (2) to determine the angle between OQ and OT as in Fig. 4. It will be observed that

the two square roots in the denominator are none other than the absolute magnitudes of the principal QRS and T axes, *OQ* and *OT*, as determined by Equation (1). Consequently, when the latter has been determined it is a very simple matter to go ahead and determine the absolute spatial angle between them.

Actually, it is not necessary to determine the rectangular coordinates of the tips of the principal QRS and T axes in order to be able to determine the spatial angle θ. Spherical trigonometry may be used to derive a solution exclusively in terms of the angles made by the vector projections of OQ and OT on any two of the three coordinate planes. After defining our angles as in Fig. 5 we may proceed by noting that α is equal to α_1 and that β is equal to β_1. The plane defined by *XOZ* still represents the frontal vectorcardiographic plane, *YOZ* the sagittal, and *XOY* the horizontal. By definition *CQZ* and *DTZ* are meridian arcs and *XCDY* is an equatorial arc. Consequently *QCY* and *TDY* are right spherical triangles. Napier's rules for the solution of right spherical triangles allows us to state that

$$\tan \mathrm{YQ} = \frac{\tan \gamma}{\cos \alpha}, \qquad \tan \mathrm{YT} = \frac{\tan \delta}{\cos(\alpha + \beta)} \tag{3}$$

We now have information about two sides, *YQ* and *YT*, and the included angle, β, of the oblique spherical triangle *QYT*. The law of cosines for oblique spherical triangles[7] states that the cosine of one side is equal to the product of the cosines of the other two sides plus the product of the sines of those two sides multiplied by the cosine of their included angle. If we substitute the values for the two known sides in Equation (3) into the above law we obtain

$$\begin{aligned} \cos \theta = {} & \cos\left[\tan^{-1}\frac{\tan \gamma}{\cos \alpha}\right] \cdot \cos\left[\tan^{-1}\frac{\tan \delta}{\cos(\alpha + \beta)}\right] \\ & + \sin\left[\tan^{-1}\frac{\tan \gamma}{\cos \alpha}\right] \cdot \sin\left[\tan^{-1}\frac{\tan \delta}{\cos(\alpha + \beta)}\right] \cdot \cos \beta \end{aligned} \tag{4}$$

Q.E.D.

Equation (4) is rather awkward, however, compared to the simplicity of Equation (2).

The above applications have concerned electrical properties of the heart whose clinical importance has been firmly established for many years. Measurements along similar lines would be the use of Equation (1) to determine the absolute spatial magnitude as well as direction of shift of any S-T vector from the isoelectric point. The absolute magnitude of an "infarction vector"[3] in myocardial infarction might be similarly studied with profit. For example, it is possible that when such a vector is directed at approximately a 45 degree angle to all three coordinate planes it may fail to seem to be of significant magnitude since it would not appear in its full length in any vectorcardiographic plane. This situation would be unmasked by quantitative spatial analysis. The same methods could be used to explore the quantitative spatial relationships between the P and QRS or T loops in such conditions as cor pulmonale or mitral stenosis, for example, using Equations (1) and (2). Another attractive possibility concerns

the development of precise standards for the evaluation of an exercise tolerance spatial vectorcardiogram. Changes in the spatial angle between the principal QRS and T axes are particularly promising as quantitative measurements which may extend the usefulness of the electrocardiographic method.

Formulations which exploit properties peculiar to the vectorcardiographic method of depicting the heart's electrical activity also suggest themselves. One such formulation consists of quantitating the degree to which the spatial QRS loop balloons out to become less narrow and elongate and more nearly circular as may occur, for example, as ventricular hypertrophy, intraventricular conduction disturbance, or myocardial infarction develops.[3] A convenient way to measure this would be to establish a ratio between the absolute length of the minor axis of the somewhat ellipsoidal figure which the QRS loop usually forms and the length of the major axis. The major axis, of course, is the same as the principal axis, *OQ*, which was determined in Equation (1). If we call (d, e, f) and (d_1, e_1, f_1) the rectangular coordinates of the extremities of the minor axis of the ellipse, called EF, then its length may be expressed by

$$EF = \sqrt{(d - d_1)^2 + (e - e_1)^2 + (f - f_1)^2} \tag{5}$$

and the ratio, r, by

$$r = \frac{\sqrt{(d - d_1)^2 + (e - e_1)^2 + (f - f_1)^2}}{\sqrt{(x^2 + y^2 + z^2)}} \tag{6}$$

Another possibly fruitful approach would be the quantitation of the degree to which parts of the QRS loop depart from the "plane of predilection" described by Vastesaeger and Rochet.[8] In normal vectorcardiograms the QRS loops tend to lie fairly well within one plane, although the spatial position of that plane may vary considerably from person to person, particularly with differing electrical positions of the heart. A certain amount of departure from the plane of predilection occurs normally, as evidenced by the figure-of-eight appearance of the QRS loop in some frontal plane vectorcardiograms, especially in subjects whose hearts are electrically intermediate in position. The degree to which the distal part of a QRS loop departs from the plane established by the proximal part could be expressed quantitatively by determining the angle between a line joining the outgoing and incoming QRS limbs at points which are equidistant from but near the isoelectric point and a similar line which is farther away from the origin.

A still more important observation of Vastesaeger and Rochet[8] which seems to have remained more or less unnoticed is that fairly vertical or horizontal normal adult hearts always show a deviation of some 30 to 40 degrees (according to their technique) between the principal QRS and T axes. They measured this on the frontal plane projection but estimated that about the same value obtained for the spatial angle. The implication is that it is actually abnormal to have the QRS and the T loops pointing in exactly the same direction in the presence of a markedly vertical or horizontal heart. This point is certainly worth exploring in a more quantitative fashion.

DISCUSSION

In the foregoing it was assumed that the P, QRS, and T loops of a vectorcardiogram are roughly elliptical in shape. Although this is usually the case, there are many instances where more bizarre shapes are encountered, particularly in the QRS loops of patients with intraventricular conduction disturbance or myocardial infarction. Failure to recognize this is a potential weakness of any method which aims to derive vectorcardiographic information by simplified construction from conventional electrocardiograms. Fortunately, it is easy to detect the presence of nonelliptical loops when actual vectorcardiography is practiced, although in these instances some of the equations and applications described above are probably not valid, or at least the results obtained may not have the same meaning.

It will certainly occur to some that the mathematical manipulations described above are too complicated for clinical use by the cardiologist. While this may be true in some instances as far as routine application is concerned, it is felt that the development of standards on large numbers of cases will prove helpful in evaluating the borderline case. Moreover, some of the formulations may be expressed in tabular form for clinical use and so be freed of some of the mathematical onus. It seems probable that to increase the precision of cardiac diagnosis by electrical means in the future, it will be necessary to rely more and more on quantitative formulations.

SUMMARY

The incorporation of a frame of reference into spatial vectorcardiograms allows one to make quantitative measurements which lend themselves readily to simple trigonometric and geometric analysis. This provides an easy way to make evaluations which take advantage of the three-dimensional character of the vectorcardiographic medium and extend the precision of several concepts developed by electrocardiography.

REFERENCES

1. Wilson, F. N., Macleod, A. G., Barker, P. S., and Johnston, F. D.: The Determination of the Significance of the Areas of the Ventricular Deflections of the Electrocardiogram, Am. Heart J. **10**:46, 1934.
2. Duchosal, P., and Sulzer, R.: La Vectocardiographie, Basel, 1949, S. Karger.
3. Grishman, A., and Scherlis, L.: Spatial Vectorcardiography, Philadelphia, 1952, W. B. Saunders Company.
4. Whipple, G. H.: A Simple Technique for Registering the Direction of Rotation of Vectorcardiographic Loops, Am. Heart J. **44**:384, 1952.
5. Sokolow, M., and Lyon, T. P.: The Ventricular Complex in Left Ventricular Hypertrophy as Obtained by Unipolar Precordial and Limb Leads, Am. Heart J. **37**:161, 1949.
6. Osgood, W. F., and Graustein, W. C.: Plane and Solid Analytic Geometry, New York, 1921, The Macmillan Company.
7. Nelson, A. L., and Folley, K. W.: Plane and Spherical Trigonometry, New York, 1936, Harper & Brothers.
8. Vastesaeger, M., and Rochet, J.: Les propriétés du vectocardiogramme spatial de l'homme normal, ses variations physiologiques, Tr. Laborat. physiol. Inst. Solvay **29** (fasc. 4):55, 1944.

A SIMPLIFIED METHOD FOR DETERMINING THE ANGLE BETWEEN TWO SPATIAL VECTORS

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FORMULAS have been recently published[1] for the calculation of the angle between two spatial vectors, given the angular positions of the vector projections on two mutually perpendicular planes. Since the trigonometric computations involved are time-consuming, we have constructed a table for their simplification. It is the purpose of this paper to make this table available and to describe the manner in which it is used. In our experience,[1] as well as that of others,[2,3] Grant's method of estimating the QRS-T angle has been difficult and probably relatively inaccurate. It is our hope that this communication will lead to a wider and more quantitative application of Grant's fundamental concept in order that its value and limitations in routine electrocardiography may be more clearly assessed. For this reason, the table has been adapted specifically to Grant's estimation of angular measurements to the closest five degrees.

The methods of making angular measurements of the positions of projected vectors have been adequately described in preceding publications.[1,4,5] Any reasonable diagram depicting the arrangement of precordial electrodes about the electrical center of the heart, as, for example, that published recently,[1] may be used for determination of the positions of vector projections on the transverse plane. The ingenious method described by Langner[2] of constructing the transverse plane according to chest measurements obtained from the patient has merit except that such data would not be available for the large number of electrocardiograms which have accumulated in the past as well as the great majority of those to be taken in the future. For the present, the adoption of a uniform diagram would seem desirable for clinical use. Methods of devising diagrams for an individual subject as well as a more rational placement of electrodes for depicting electrical forces in the transverse plane belong in the realm of research.

Table I was constructed for measurements to be made as described and illustrated in the preceding paper.[1] A separate axis is used as the axis of reference for each plane (Fig. 1). In the transverse plane, viewed in a head-foot direction with the subject prone, angular measurements are made in a clockwise direction from the posterior end of the anterior-posterior axis. In the frontal plane, viewed in an anterior-posterior direction with the subject upright, angular measurements

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are made in a clockwise direction from the (subject's) left end of the horizontal (Lead I) axis. Both of these measurements may be made through a range of 360°. For the first vector, for example that of QRS, the angle measured in the transverse plane is located in the horizontal marginal columns at the top of Table I, and the angle measured in the frontal plane is located in the vertical marginal columns at the left of this table.* The three numbers located at the intersection of the columns are read directly from the table. Positive or negative signs are given to these three values according to the signs listed in parentheses in the marginal columns. The two signs obtained from the horizontal marginal column are placed before the upper and middle numbers respectively. The two signs obtained from the vertical marginal column are placed before the middle and lower numbers respectively. Thus the sign of the middle number may be obtained in two different ways. Failure of these signs to coincide indicates some defect in the angular measurements.

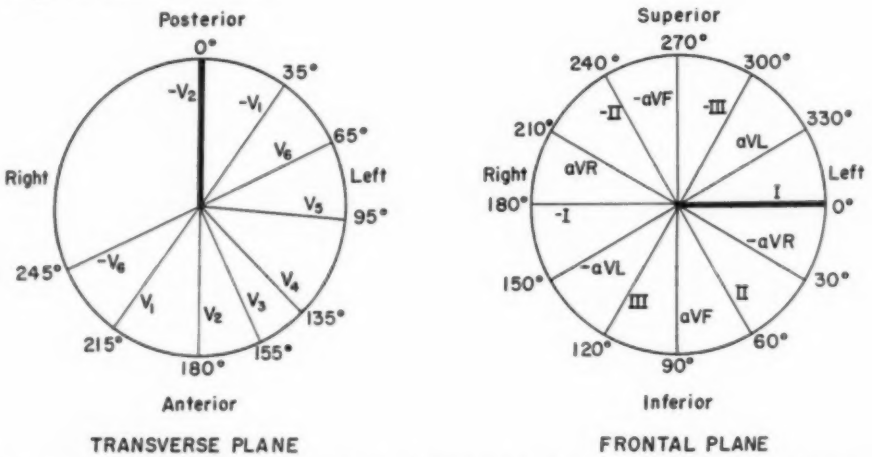

Fig. 1.—Diagrams showing axes of reference for measuring the angular positions of vectors projected on the transverse and frontal planes. The diagram for the transverse plane has been constructed from a cross-section anatomical drawing.[1] The diagram for the frontal plane is the hexaxial reference system.[5] See text.

The angles measured in the transverse and frontal planes of the second vector, for example that of T, are likewise determined and located in the horizontal and vertical marginal columns, respectively. In the same manner the three values located at the intersection of these columns are read from Table I and the proper signs given to each. Two sets of three values are thus obtained, one set for each vector. The respective products of the paired upper values, of the paired middle values, and of the paired lower values are obtained by multiplication. Proper signs are given to these three products in accordance with the well-known rule that multiplication of numbers with like signs yields a product which is positive,

*If a spatial reference frame of a type which permits measurement of the angular positions of vector projections on the sagittal plane is used, such measurements may replace those of either the transverse or the frontal planes. The measurements on the sagittal plane must be made in accord with the directions given in the preceding paper.[1] The following scheme should be followed in choosing the proper horizontal or vertical marginal columns of Table I for locating angular values measured on any two mutually perpendicular planes: 1. Frontal plane (horizontal) and sagittal plane (vertical). 2. Sagittal plane (horizontal) and transverse plane (vertical). 3. Transverse plane (horizontal) and frontal plane (vertical).

TABLE I*

	0° (++) 180° (−+) 180° (−−) 360° (+−)	5° (++) 175° (−+) 185° (−−) 355° (+−)	10° (++) 170° (−+) 190° (−−) 350° (+−)	15° (++) 165° (−+) 195° (−−) 345° (+−)	20° (++) 160° (−+) 200° (−−) 340° (+−)	25° (++) 155° (−+) 205° (−−) 335° (+−)	30° (++) 150° (−+) 210° (−−) 330° (+−)	35° (++) 145° (−+) 215° (−−) 325° (+−)	40° (++) 140° (−+) 220° (−−) 320° (+−)	45° (++) 135° (−+) 225° (−−) 315° (+−)	50° (++) 130° (−+) 230° (−−) 310° (+−)	55° (++) 125° (−+) 235° (−−) 305° (+−)	60° (++) 120° (−+) 240° (−−) 300° (+−)	65° (++) 115° (−+) 245° (−−) 295° (+−)	70° (++) 110° (−+) 250° (−−) 290° (+−)	75° (++) 105° (−+) 255° (−−) 285° (+−)	80° (++) 100° (−+) 260° (−−) 280° (+−)	85° (++) 95° (−+) 265° (−−) 275° (+−)	90° (++) 90° (−+) 270° (−−) 270° (+−)
cos = 1.000																			
0°(++)																			
180°(−+)	1.00	1.00	.98	.97	.94	.91	.87	.82	.77	.71	.64	.57	.50	.42	.34	.26	.17	.09	.00
180°(−−)	.00	.09	.17	.26	.34	.42	.50	.57	.64	.71	.77	.82	.87	.91	.94	.97	.98	1.00	1.00
360°(+−)	.00	.00	.00	.00	.00	.00	.00	.00	.00	.00	.00	.00	.00	.00	.00	.00	.00	.00	.00
cos = .9994																			
5°(++)																			
175°(−+)	1.00	1.00	.98	.97	.94	.91	.87	.82	.76	.71	.64	.57	.50	.42	.34	.26	.17	.09	.00
185°(−−)	.00	.09	.17	.26	.34	.42	.50	.57	.64	.71	.76	.82	.86	.90	.94	.96	.98	.99	1.00
355°(+−)	.00	.01	.02	.02	.03	.04	.04	.05	.06	.06	.07	.07	.08	.08	.08	.08	.09	.09	.09
cos = .991																			
10°(++)																			
170°(−+)	1.00	1.00	.98	.96	.94	.90	.86	.81	.76	.70	.64	.57	.49	.42	.34	.26	.17	.09	.00
190°(−−)	.00	.09	.17	.26	.34	.42	.50	.57	.64	.70	.76	.81	.86	.89	.93	.95	.97	.98	.98
350°(+−)	.00	.02	.03	.05	.06	.07	.09	.10	.11	.12	.13	.14	.15	.16	.16	.17	.17	.17	.17
cos = .976																			
15°(++)																			
165°(−+)	1.00	1.00	.98	.96	.94	.90	.86	.81	.75	.69	.63	.56	.49	.41	.33	.25	.17	.08	.00
195°(−−)	.00	.09	.17	.26	.34	.42	.50	.57	.63	.69	.75	.80	.84	.88	.91	.94	.95	.96	.97
345°(+−)	.00	.02	.05	.07	.09	.11	.13	.15	.17	.19	.20	.21	.23	.24	.24	.25	.26	.26	.26
cos = .954																			
20°(++)																			
160°(−+)	1.00	1.00	.98	.96	.93	.90	.85	.80	.75	.68	.62	.55	.48	.40	.32	.24	.16	.08	.00
200°(−−)	.00	.09	.17	.26	.34	.42	.49	.56	.63	.68	.74	.79	.83	.86	.89	.91	.93	.94	.94
340°(+−)	.00	.03	.06	.09	.12	.15	.18	.20	.23	.25	.27	.29	.30	.31	.32	.33	.34	.34	.34
cos = .924																			
25°(++)																			
155°(−+)	1.00	1.00	.98	.96	.93	.89	.84	.79	.73	.67	.61	.54	.46	.39	.31	.24	.16	.08	.00
205°(−−)	.00	.09	.17	.26	.34	.41	.49	.55	.62	.67	.72	.77	.80	.83	.86	.88	.89	.90	.91
335°(+−)	.00	.04	.08	.12	.16	.19	.23	.26	.29	.31	.34	.36	.37	.39	.40	.41	.42	.42	.42

*See text for description of the method of applying this table for the calculation of the angle between two spatial vectors.

TABLE I (CONTINUED)

	0° (++)	5° (++)	10° (++)	15° (++)	20° (++)	25° (++)	30° (++)	35° (++)	40° (++)	45° (++)	50° (++)	55° (++)	60° (++)	65° (++)	70° (++)	75° (++)	80° (++)	85° (++)	90° (++)
	180° (−+)	175° (−+)	170° (−+)	165° (−+)	160° (−+)	155° (−+)	150° (−+)	145° (−+)	140° (−+)	135° (−+)	130° (−+)	125° (−+)	120° (−+)	115° (−+)	110° (−+)	105° (−+)	100° (−+)	95° (−+)	90° (−+)
	180° (−−)	185° (−−)	190° (−−)	195° (−−)	200° (−−)	205° (−−)	210° (−−)	215° (−−)	220° (−−)	225° (−−)	230° (−−)	235° (−−)	240° (−−)	245° (−−)	250° (−−)	255° (−−)	260° (−−)	265° (−−)	270° (−−)
	360° (+−)	355° (+−)	350° (+−)	345° (+−)	340° (+−)	335° (+−)	330° (+−)	325° (+−)	320° (+−)	315° (+−)	310° (+−)	305° (+−)	300° (+−)	295° (+−)	290° (+−)	285° (+−)	280° (+−)	275° (+−)	270° (+−)
cos = .887																			
30°(++)																			
150°(−+)	1.00	.99	.98	.96	.92	.88	.83	.78	.72	.65	.59	.52	.45	.37	.30	.23	.15	.08	.00
210°(−−)	.00	.09	.17	.26	.34	.41	.48	.54	.60	.65	.70	.74	.77	.80	.83	.84	.86	.86	.87
330°(+−)	.00	.05	.10	.15	.19	.24	.28	.31	.35	.38	.40	.43	.45	.46	.48	.49	.49	.50	.50
cos = .843																			
35°(++)																			
145°(−+)	1.00	.99	.98	.95	.91	.87	.82	.76	.70	.63	.57	.50	.43	.36	.29	.21	.14	.07	.00
215°(−−)	.00	.09	.17	.25	.33	.41	.47	.53	.59	.63	.68	.71	.74	.77	.79	.80	.81	.82	.82
325°(+−)	.00	.06	.12	.18	.23	.28	.33	.37	.41	.44	.47	.50	.52	.54	.55	.56	.57	.57	.57
cos = .793																			
40°(++)																			
140°(−+)	1.00	.99	.97	.94	.90	.85	.80	.74	.67	.61	.54	.47	.40	.34	.27	.20	.13	.07	.00
220°(−−)	.00	.09	.17	.25	.33	.40	.46	.52	.57	.61	.64	.68	.70	.72	.74	.75	.76	.76	.77
320°(+−)	.00	.07	.14	.21	.28	.33	.39	.43	.47	.51	.54	.57	.59	.61	.62	.63	.64	.64	.64
cos = .737																			
45°(++)																			
135°(−+)	1.00	.99	.97	.94	.89	.83	.77	.71	.64	.58	.51	.44	.38	.31	.25	.19	.12	.06	.00
225°(−−)	.00	.09	.17	.25	.32	.39	.45	.50	.54	.58	.61	.63	.65	.67	.68	.69	.70	.71	.71
315°(+−)	.00	.09	.17	.25	.32	.39	.45	.50	.54	.58	.61	.63	.65	.67	.68	.69	.70	.71	.71
cos = .676																			
50°(++)																			
130°(−+)	1.00	.99	.96	.92	.87	.81	.74	.68	.61	.54	.47	.41	.35	.29	.23	.17	.11	.06	.00
230°(−−)	.00	.09	.17	.25	.32	.38	.43	.47	.51	.54	.57	.59	.60	.62	.63	.63	.64	.64	.64
310°(+−)	.00	.10	.20	.29	.38	.45	.51	.56	.61	.64	.67	.70	.72	.73	.75	.75	.76	.76	.77
cos = .609																			
55°(++)																			
125°(−+)	1.00	.99	.96	.91	.84	.78	.70	.63	.56	.50	.43	.37	.31	.26	.20	.15	.10	.05	.00
235°(−−)	.00	.09	.17	.24	.31	.36	.41	.44	.47	.50	.52	.53	.54	.55	.56	.57	.57	.57	.57
305°(+−)	.00	.12	.24	.35	.44	.52	.58	.63	.68	.71	.74	.76	.78	.79	.80	.81	.81	.82	.82

cos = .537																			
60°(++)																			
120°(−+)	1.00	.99	.94	.88	.81	.73	.65	.58	.51	.45	.39	.33	.28	.23	.18	.13	.09	.04	.00
240°(−−)	.00	.09	.17	.24	.29	.34	.38	.41	.43	.45	.46	.47	.48	.49	.49	.50	.50	.50	.50
300°(+−)	.00	.15	.29	.41	.51	.59	.65	.70	.74	.77	.80	.82	.83	.84	.85	.86	.86	.87	.87
cos = .462																			
65°(++)																			
115°(−+)	1.00	.98	.92	.84	.76	.67	.59	.52	.45	.39	.33	.28	.24	.19	.15	.11	.07	.04	.00
245°(−−)	.00	.09	.16	.23	.28	.31	.34	.36	.38	.39	.40	.41	.41	.41	.42	.42	.42	.42	.42
295°(+−)	.00	.18	.35	.49	.59	.67	.73	.78	.81	.83	.85	.87	.88	.89	.90	.90	.90	.91	.91
cos = .383																			
70°(++)																			
110°(−+)	1.00	.97	.89	.79	.68	.59	.51	.44	.38	.32	.28	.23	.19	.16	.12	.09	.06	.03	.00
250°(−−)	.00	.08	.16	.20	.25	.28	.29	.31	.32	.32	.33	.33	.34	.34	.34	.34	.34	.34	.34
290°(+−)	.00	.23	.43	.58	.68	.76	.81	.84	.87	.89	.90	.91	.92	.93	.93	.94	.94	.94	.94
cos = .301																			
75°(++)																			
105°(−+)	1.00	.95	.83	.69	.58	.49	.41	.35	.29	.25	.21	.18	.15	.12	.09	.07	.05	.02	.00
255°(−−)	.00	.08	.15	.19	.20	.23	.24	.24	.25	.25	.25	.25	.26	.26	.26	.26	.26	.26	.26
285°(+−)	.00	.31	.54	.69	.79	.84	.88	.91	.92	.94	.94	.95	.96	.96	.96	.96	.96	.97	.97
cos = .216																			
80°(++)																			
100°(−+)	1.00	.89	.70	.54	.43	.35	.29	.24	.20	.17	.14	.12	.10	.08	.06	.05	.03	.02	.00
260°(−−)	.00	.08	.12	.15	.16	.16	.17	.17	.17	.17	.17	.17	.17	.17	.17	.17	.17	.17	.17
280°(+−)	.00	.44	.70	.83	.89	.92	.94	.96	.96	.97	.97	.98	.98	.98	.98	.98	.98	.98	.98
cos = .131																			
85°(++)																			
95°(−+)	1.00	.71	.44	.31	.23	.18	.15	.12	.10	.09	.07	.06	.05	.04	.03	.02	.02	.01	.00
265°(−−)	.00	.06	.08	.08	.08	.09	.09	.09	.09	.09	.09	.09	.09	.09	.09	.09	.09	.09	.09
275°(+−)	.00	.71	.89	.95	.97	.98	.99	.99	.99	.99	.99	.99	.99	1.00	1.00	1.00	1.00	1.00	1.00
cos = .044																			
90°(++)																			
90°(−+)	—	.00	.00	.00	.00	.00	.00	.00	.00	.00	.00	.00	.00	.00	.00	.00	.00	.00	.00
270°(−−)	.00	.00	.00	.00	.00	.00	.00	.00	.00	.00	.00	.00	.00	.00	.00	.00	.00	.00	.00
270°(+−)	—	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
cos = .000																			

and multiplication of numbers with unlike signs yields a product which is negative. The three products are then added algebraically according to their signs. The result is the cosine of the angle between the two spatial vectors. In Table I, cosines for values midway between the groups of angles given in the vertical marginal columns are listed. By locating in these columns the position of the calculated cosine, the spatial angle may be read to the nearest 5 degrees. If the calculated cosine is positive, the angle chosen must be between 0° and 90°. If the calculated cosine has a negative value, the angle chosen must be between 90° and 180°. The angle between two spatial vectors cannot exceed 180°.

In order to illustrate the arithmetical manipulations involved, an example is given below. This is taken from the previous paper (Subject 19, Table I)[1] and is chosen especially to demonstrate the assignment of the proper positive and negative signs to angles larger than 90°.

	Transverse	*Frontal*
QRS	55°	330°
T	135°	15°

From Table I:

	QRS		*T*	
(1)	+.52	×	−.69	= −.3588
(2)	+.74	×	+.69	= +.5106
(3)	−.43	×	+.19	= −.0817
				+.0701 = cos of spatial angle

Spatial angle = 85°

After the fundamental manipulations are mastered, the time required for the calculation of an angle between two spatial vectors from angular positions of their projections on two mutually perpendicular planes is relatively negligible in the complete vector analysis of an electrocardiographic tracing. Although we have had no experience with the geometric method of determination of a spatial angle with the aid of a model,[2] the trigonometric method, as herein described, is in our opinion much more convenient and better adapted to routine application.

In order to maintain simplicity, the fundamental accuracy of the trigonometric method has been slightly reduced by rounding off the values obtained from Table I to the closest second decimal place. However, we believe that, in most instances, the accuracy of the transformations made with the table will far exceed the accuracy of the values with which the table is entered.

REFERENCES

1. Helm, R. A., and Fowler, N. O., Jr.: Studies on the QRS-T Angle, Am. Heart J. 1953.
2. Langner, P. H., Jr.: A Geometric Model for Determining the Direction of Mean Spatial Vectors, Am. Heart J. **44**:378, 1952.
3. Urschel, D. L., and Abbey, D. C.: Modification of a Vector Model to Provide Accurate Recording of Mean Vector Positions in Three Planes of Space, Am. Heart J. **44**:372, 1952.
4. Grant, R. P., and Estes, E. H.: Spatial Vector Electrocardiography, Philadelphia, 1951, The Blakiston Company.
5. Graettinger, J. S., Packard, J. M., and Graybiel, A.: A New Method of Equating and Presenting Bipolar and Unipolar Extremity Leads of the Electrocardiogram, Am. J. Med. **11**:3, 1951.

SPATIAL VECTOR ANALYSIS OF EARLY RIGHT VENTRICULAR PREPONDERANCE

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SINCE Kahn[1] drew attention to the peaked P wave in patients with pulmonary emphysema, later called "P pulmonale" by Winternitz,[2] many advances in the definition of the electrocardiographic picture seen in this disease have been accomplished. Precordial and unipolar limb leads have aided a great deal, especially in the definition of right ventricular hypertrophy. However, typical right ventricular strain changes are seen clinically only in patients with far advanced pulmonary disease.

In order to define the more subtle changes that must occur before the classical right ventricular strain develops, multiple chest leads and stereovectorcardiograms were studied in a group of sixteen patients with severe to incapacitating chronic pulmonary emphysema.

MATERIAL

A group of sixteen men whose average age was 55 with pulmonary emphysema was studied. The subjects were moderately to completely incapacitated by their disease. The diagnosis was established by a history of chronic respiratory difficulty, physical findings, low vital capacity with a slow expiratory phase, and roentgenogram findings of pulmonary emphysema. Twelve of the sixteen had compensated respiratory acidosis as indicated by a high carbon dioxide combining power. Three of the sixteen patients had evidence of cardiac decompensation as a result of their pulmonary disease at the time that they were studied.

None of the patients was receiving digitalis at the time of the study or had complicating cardiovascular disease, such as hypertensive cardiovascular disease or rheumatic heart disease. Patients with angina of effort and electrocardiographic changes of myocardial ischemia were excluded, with the exception of one patient who had T-wave changes in the precordial leads.

A group of nineteen individuals of comparable age without clinical or laboratory evidence of either cardiovascular or pulmonary disease served as controls.

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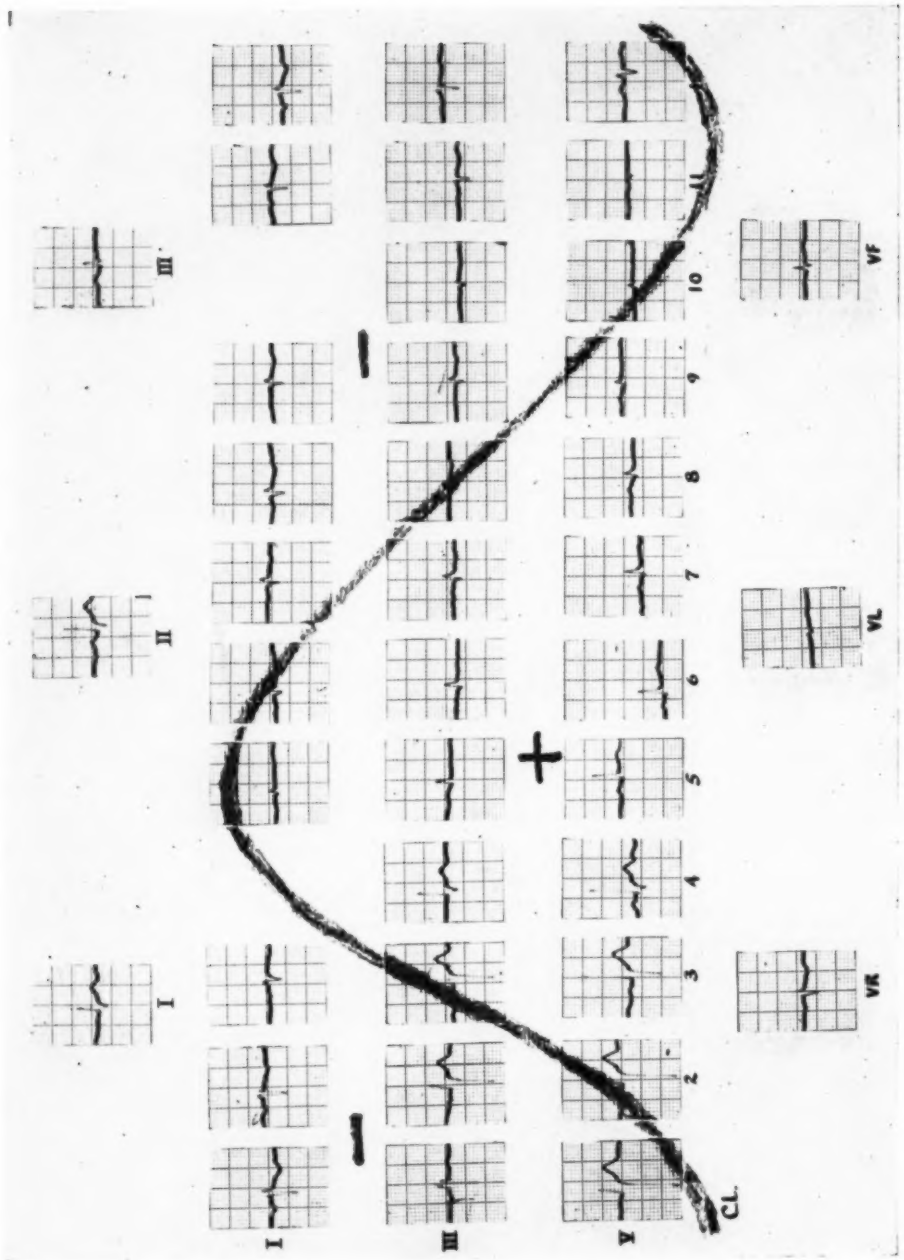

Fig. 1.—Chart showing the distribution of potentials which are at the first, third, and fifth intercostal spaces anteriorly together with the QRS null contour drawn.

METHOD

With direct writing equipment and the subject in a sitting position electrocardiograms were taken in the following manner: (1) bipolar extremity leads, (2) unipolar extremity leads, (3) precordial leads taken concentrically at the first, third, and fifth intercostal spaces at the sternum. These are designated by Roman numerals I, III and V, respectively, as shown in Fig. 1. Arabic numerals *1* to *12* as seen in Fig. 1 represent the placement of the exploring electrode concentrically about the chest starting with number one at the midsternal line. Two is at a mid-point between the left anterior axillary line and the midsternal line. Three is at the left anterior axillary line. Four is at the left midaxillary line. Five is at the left posterior axillary line. Six is at a mid-point between the spine and the left posterior axillary line. Seven is at the spine. Eight through twelve are at comparable anatomic positions over the right hemithorax as described above for the left hemithorax. Leads at the right and left midaxillary line were not obtained at the first level. Therefore, precordial leads were obtained at thirty-four different chest locations which produced three parallel, horizontal planes in the first, third, and fifth intercostal spaces at the sternum.

One representative complex of each lead was mounted as represented in Fig. 1. The subjects with pulmonary emphysema as well as the control subjects were divided into four separate groups determined by the QRS electrical axis in the frontal plane. These groups were as follows: horizontal or left axis, 0 degree or less; intermediate axis, 0 to +60 degrees; vertical axis, +60 to +95 degrees; and right ventricular preponderance, greater than +95 degrees. The division of the material is shown in Table I.

TABLE I. DISTRIBUTION OF MATERIAL

	PULMONARY EMPHYSEMA (NO. OF SUBJECTS)	CONTROL (NO. OF SUBJECTS)
Horizontal axis	0	5
Intermediate axis	3	7
Vertical axis	8	7
Right ventricular preponderance	5	0

In order to delineate differences in pattern distribution graphically of the various groups, null contour lines were determined from the location of equiphasic P, QRS, and T deflections as described by Grant.[3] These contour lines of the subjects in the individual groups are noted in Figs. 1, 2, and 3. For clarity of presentation and for comparative purposes, the null contour curves were not superimposed upon the electrocardiograms but on blanks of proportional size and distribution of the originally mounted electrocardiograms. Each curve represents the graphic orientation of the zones of electrical positivity and negativity. The plus signs designate areas of positive potentials, and conversely, the minus signs represent zones in which there are negative potentials. The null contour was determined for the P, QRS, and T waves of each subject.

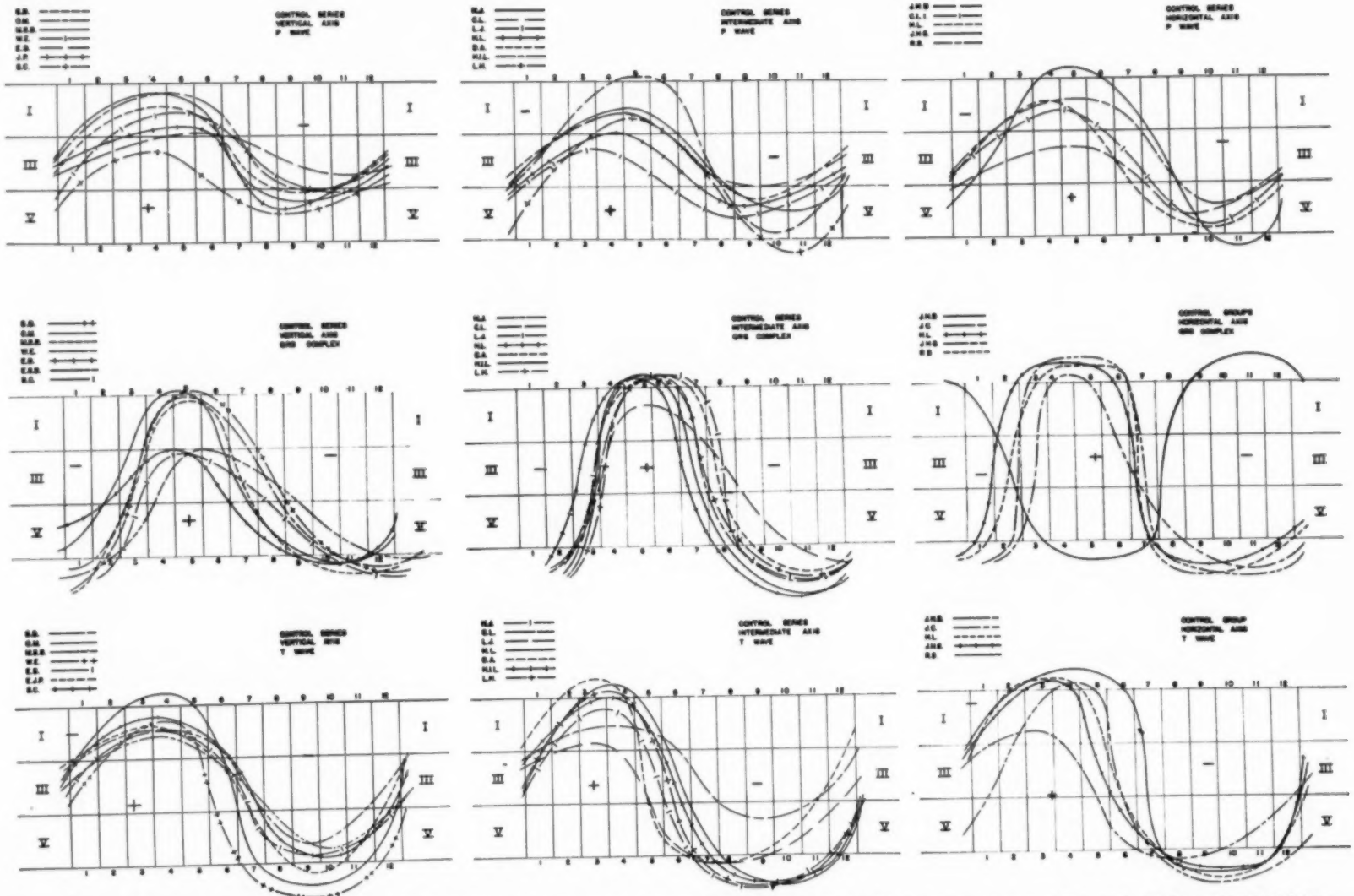

Fig. 2.—Charts showing the null contour in the control subjects of the P wave in the upper row, QRS in the center row and T wave in the lower row and from left to right those subjects with a vertical axis in the first column, intermediate axis in the middle column, and those with a horizontal axis are at the right.

Fig. 2.—Charts showing the null contour in the control subjects of the P wave in the upper row, QRS in the center row and T wave in the lower row and from left to right those subjects with a vertical axis in the first column, intermediate axis in the middle column, and those with a horizontal axis are at the right.

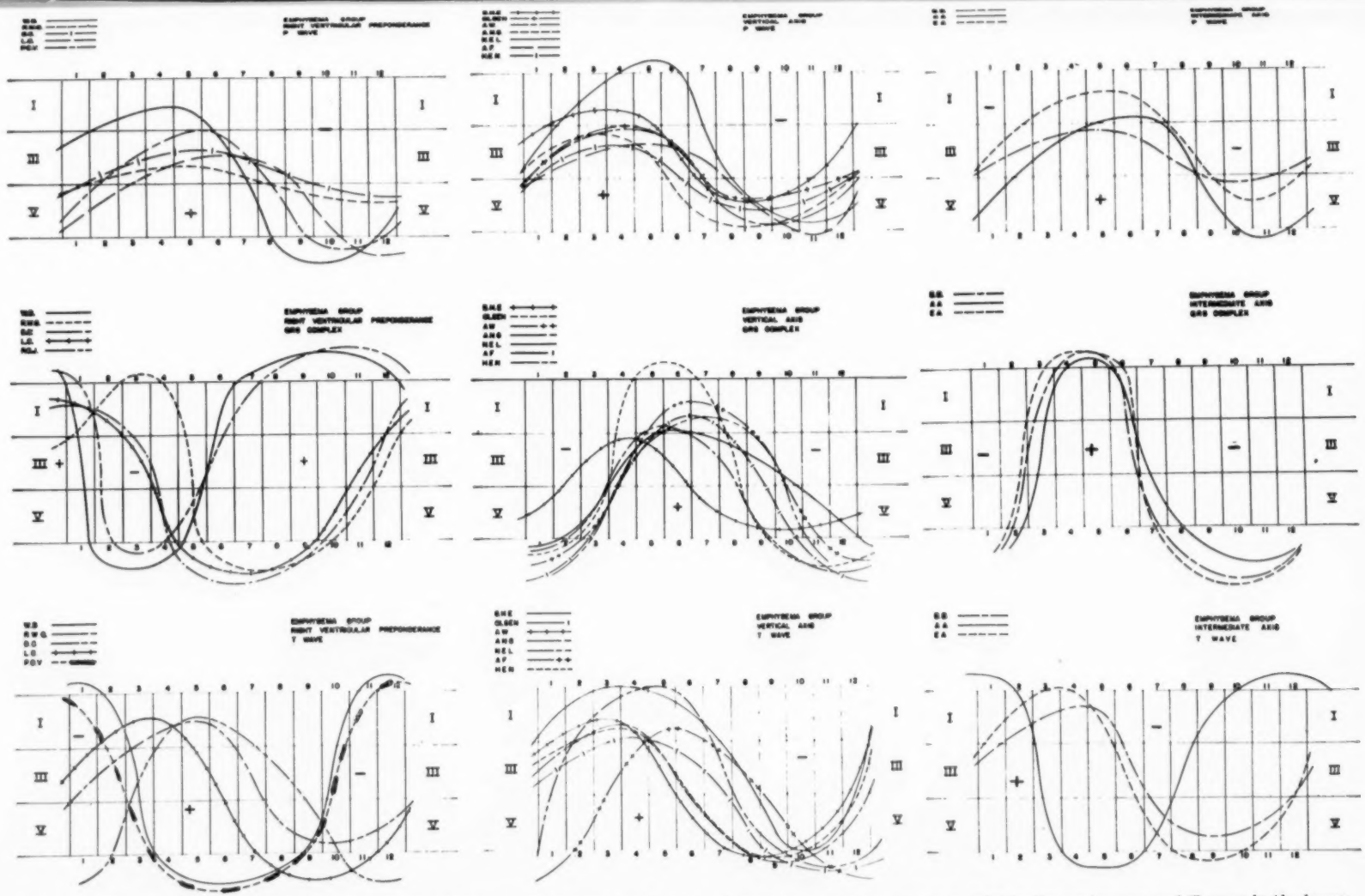

Fig. 3.—Charts showing the null contour in the subjects with pulmonary emphysema of the P wave in the upper row, QRS in the center row and T wave in the lower row, and from left to right those subjects with right ventricular preponderance in the first column, vertical axis in the middle column, and those with an intermediate axis are at the right.

Using the horizontal plane silhouette of the chest, developed by Simonson[4] which represents the horizontal plane of the chest of the fifth intercostal space anteriorly, the direction of the mean P, QRS, and T vector was determined. This was done by connecting the points produced by the null contour plane as it bisects the horizontal plane at the level of the fifth intercostal space. By definition the direction of the mean vector, in a particular plane, is perpendicular to the plane produced by the null contour, or in this case, a line connecting the two points as produced by the null contour as it crosses the level of the fifth intercostal space.

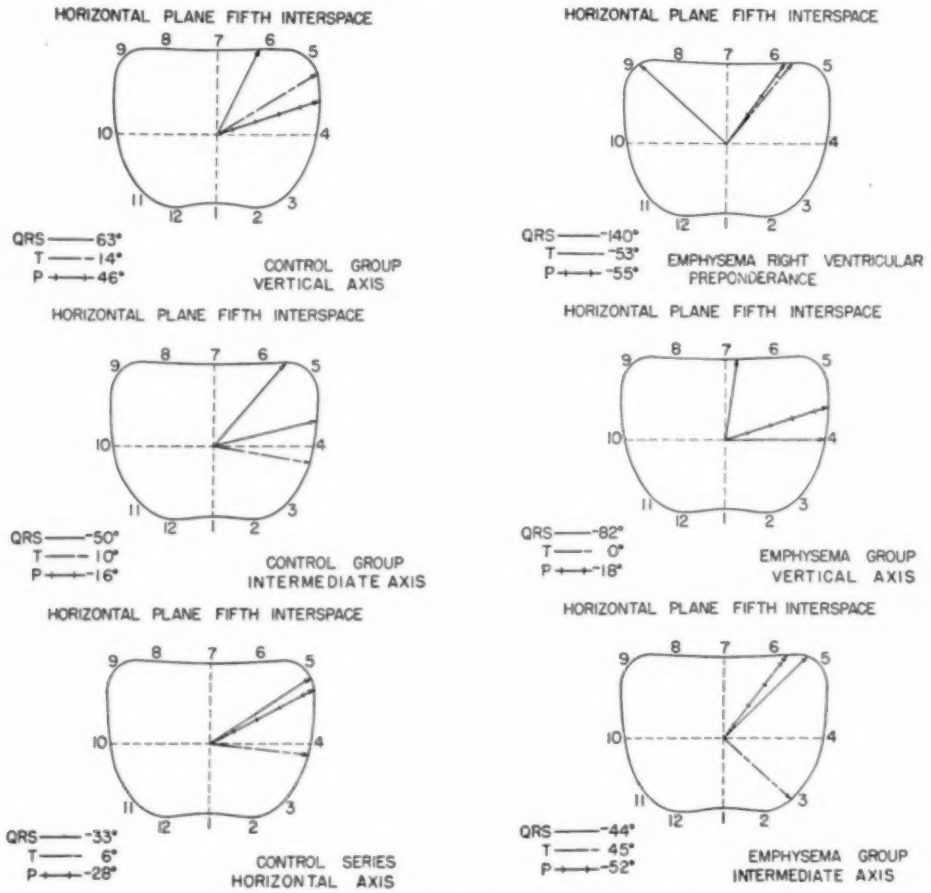

Fig. 4.—Charts showing the direction of the average of the mean P, QRS, and T vectors in the horizontal plane at the fifth intercostal space of control subjects at the left and those with pulmonary emphysema are at the right.

This level represents the *edge on view* of the null contour plane at this level. The vectors representing the direction of the mean P, QRS and T complexes in the horizontal plane are noted in Fig. 4. These figures represent the average mean P, QRS, and T vectors of the various groups as determined by the angles produced in the horizontal plane by each mean P, QRS, and T vector with respect to arbitrary reference coordinates drawn along the +90 degrees to −90 degrees axis and the 0 to 180 degrees axis.

Spatial stereovectorcardiograms were obtained by the method and instrument developed by Drs. O. Schmitt and R. Levine[5,6] of the University of Minnesota Biophysics Department. Wire loop models were constructed, by stereovisualization of the loops in various planes, from photographs taken of the stereooscilloscopes of this instrument. No quantitative measurements were made due to the errors inherent in the construction of these loops.

RESULTS

Comparing the null contour curves of the QRS complex, as noted in Figs. 2 and 3, it is noted that within each group there is uniformity of the general shape and location of the null curve with the exception of those subjects with right ventricular preponderance. All other subjects within an individual group compared very well. However, there are distinct differences when the various groups are compared. The most marked changes are seen in the subjects within the group with pulmonary emphysema and right ventricular preponderance. These curves indicate increasing areas of positive potentials of the right posterior, lateral and anterior chest (a qR pattern of the electrocardiogram); whereas the negative potentials (rS patterns on the electrocardiogram) are limited to the anterior and left chest areas. This shift to the right of the zone of positive potentials is seen to a lesser extent in the group of subjects with pulmonary emphysema and a vertical QRS axis. The descending limb of the curve falls farther to the right than that of the control group with a vertical axis. Thus, as indicated by these curves, there is a gradual shift of the zone of positive potentials, which will include more of the area of the right posterior lateral and anterior chest. One can visualize, with this shift of positive QRS potentials to the right lateral and anterior chest and shift of negative potentials to the left, the mean QRS vector in the horizontal plane will be directed to the right. This is graphically illustrated in Fig. 4 which refers to the average of the mean P, QRS, and T vectors. It should be noted that there is a gradual shift to the right of the mean QRS vector with the most marked shift noted in those subjects with pulmonary emphysema and right ventricular preponderance and the least in the control series with left axis deviation.

The T- and P-wave changes are not as remarkable when the various groups are compared with two exceptions. In the group with right ventricular preponderance, two of the T-wave curves are very similar in contour to the QRS curve but opposite in sign. This is in keeping with the classical definition of a strain pattern; namely, the mean QRS and T vectors are opposite one another. The routine electrocardiograms in these cases were the only classic right ventricular strain patterns presented in this series. The T-wave contour in one of the subjects with pulmonary emphysema and an intermediate axis differs due to the presence of a negative T wave in V_5 and V_6 in the routine electrocardiogram.

The average mean T- and P-wave vectors in the horizontal plane noted in Fig. 4 show no definite trends; however, the direction of the T-wave vector in the group of emphysema subjects with a vertical axis varies considerably from that of the control group with a vertical axis. This will be discussed in more detail later.

TABLE II. AVERAGE MEAN P, QRS AND T VECTORS IN THE FRONTAL AND HORIZONTAL PLANE

	COMPLEXES	FRONTAL PLANE (DEGREES)	HORIZONTAL PLANE (DEGREES)
Control group, horizontal or left axis	P	+45	−28
	QRS	−15	−33
	T	+28	+ 6
Control group, intermediate axis	P	+54	−16
	QRS	+28	−50
	T	+34	+10
Control group, vertical axis	P	+64	−17
	QRS	+70	−63
	T	+26	−31
Emphysema, intermediate axis	P	+64	−52
	QRS	+27	−44
	T	+79	+45
Emphysema, vertical axis	P	+80	−18
	QRS	+88	−82
	T	+57	± 0
Emphysema, right ventricular preponderance	P	+69	−55
	QRS	±180	−140
	T	+51	−53

Table II summarizes the average mean P, QRS, and T vectors in the frontal and horizontal plane.

Referring to Table II it is evident that there is a gradual but definite vertical, posterior and rightward displacement of the mean QRS vector. The P-wave vector becomes more vertical and the T-wave vector also becomes somewhat more vertical in the frontal plane with the horizontal shifts as noted previously, but the differences are probably not significant.

Figs. 5, 6, and 7 show the representative wire loop models of the stereovectorcardiograms. In the subjects with right ventricular preponderance and to a lesser extent in those patients with pulmonary emphysema and a vertical axis, there is an increasing proportion of the terminal QRS loop found to lie in the posterior right quadrant. It is to be noted that none of the subjects in the control series showed this displacement. The changes of the P- and T-wave loops could not be evaluated because of their relatively small size.

DISCUSSION

The heart in chronic pulmonary disease is classically considered as a small heart. This concept has arisen as a result of clinical, roentgenologic, and pathologic studies. Only a small percentage of patients exhibit cardiomegaly by the above criteria.

It is well appreciated that patients with chronic pulmonary disease lose considerable amounts of weight. Also it has likewise been reported that in starvation[7] or other wasting diseases such as carcinomatosis[8] the weight of the heart decreases remarkably.

An interesting pathologic study by Higgins[9] has shown that patients with chronic pulmonary disease have an increased heart weight, if the heart weight is compared to the over-all body mass, but a decreased or normal heart weight if the weight is compared with the subject's age. The latter is the classical method of determining normality of heart weight. This increase in heart weight consists mainly of an increased mass of the right ventricle. This was determined by careful dissection of the right and left ventricles and weighing them separately.

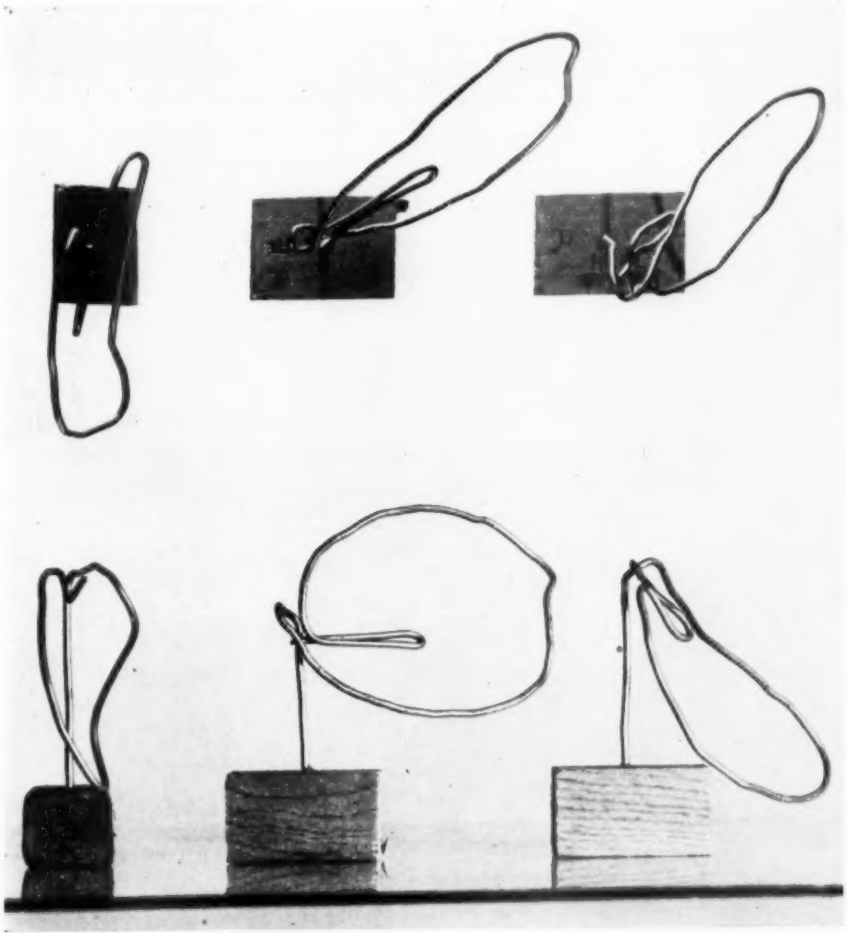

Fig. 5.—Wire loop models of stereovectorcardiograms are presented in the horizontal plane above the frontal plane below and from left to right vertical, intermediate, and horizontal axis of three control group subjects.

At birth the ratio of the right to the left ventricular muscle mass is about 3:2; whereas with increasing age the left ventricle becomes increasingly prominent so that in adult life the average ratio is 1.7:1 to 2:1, the left ventricle being greater than the right ventricle. Higgins[9] found in his studies that, with chronic pulmonary disease, the average ratio decreased to 1.3:1, and in most cases of fifteen to twenty years' duration a ratio of 1:1 existed. Hence, with, chronic pulmonary

disease the situation becomes analagous to infancy; namely, a disproportionate increase in the right ventricular muscle mass or right ventricular preponderance.

The volume of electrocardiographic literature discussing right ventricular strain and hypertrophy during the past ten years is witness to the complexity of this subject.[10-16] The following are the basic lines of reasoning that have been used: (1) QRS changes such as relatively high R waves over the right precordium; (2) T-wave changes of the right precordial and limb leads; (3) combinations of (1) and (2).

Myers and associates,[12] Oglesby and associates,[16] Johnson[17] and others have shown the necessity of additional leads to elucidate the presence of right ventricular preponderance or right ventricular strain. Simonson[4] has recently cautioned against relying on the finding of a qR pattern in the right posterior chest as being sufficient to diagnose right ventricular preponderance electrocardiographically.

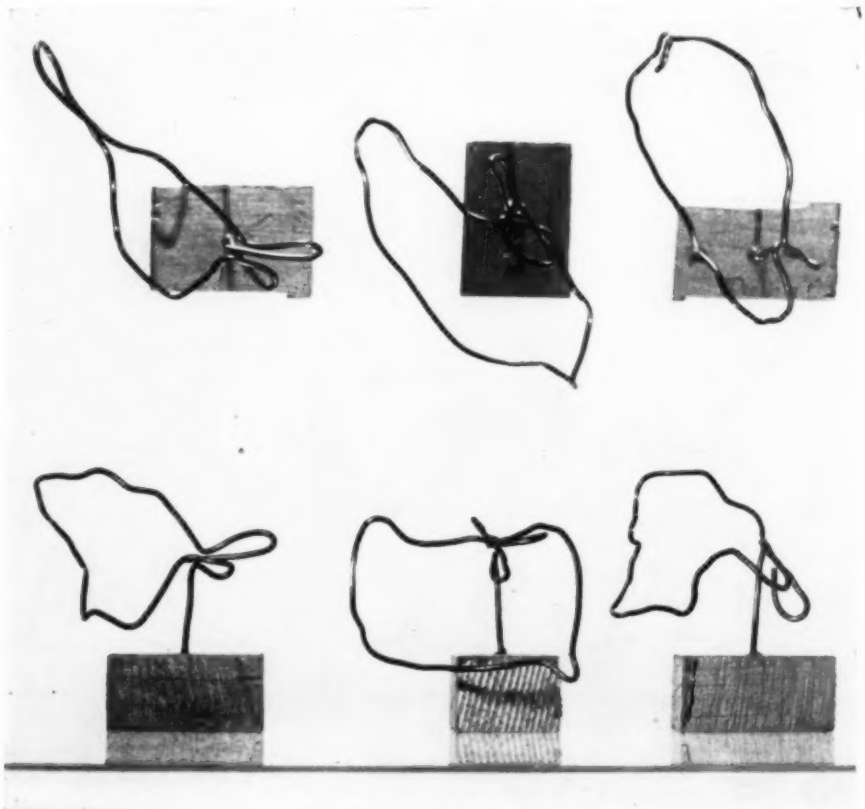

Fig. 6.—Wire loop models of the stereovectorcardiograms are presented in the horizontal plane above the frontal plane below of three subjects with right ventricular preponderance.

As noted previously, the mean QRS vector in patients with chronic pulmonary emphysema gradually rotates (counterclockwise) from posterior to anterior through the right posterior lateral and lateral quadrants as noted in Fig. 4. Therefore, the pattern distribution will change so that the qR pattern ordinarily

seen at the spine and no farther to the right than the posterior axillary line in 95 per cent of the normal population will be found in the posterior lateral and anterior chest depending upon the degree of shift of the mean QRS vector. These changes of the mean QRS vector also can be demonstrated by referring to Figs. 6 and 7, the wire loop models.

Lasser and associates[18] and Kimura[19] have described the changes of the spatial loops in right ventricular hypertrophy as being initially the displacement of the terminal portion of the QRS loop to the right posteriorly and superiorly. With increasing right ventricular preponderance, more and more of the QRS loop appeared to the right of the isoelectric point of the complex; and consequently, there is a forward rotation of the bulk of the QRS loop. This results in the for-

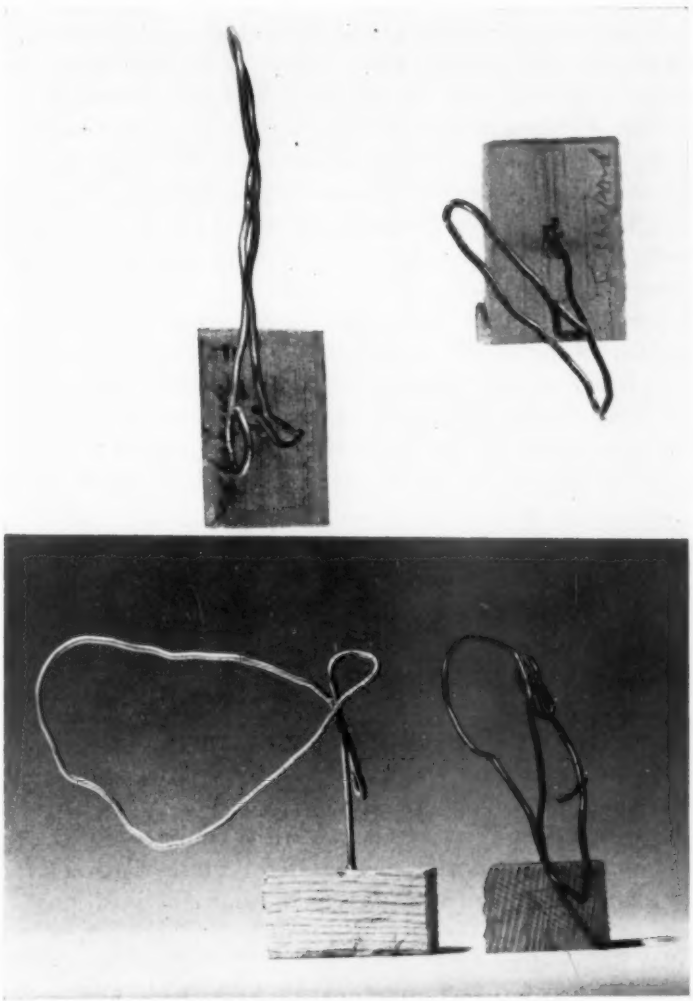

Fig. 7.—Wire loop models of the stereovectorcardiograms are presented of two subjects with pulmonary emphysema and a vertical axis, above showing the horizontal plane while below a right chest view of one subject at the left and frontal view of a different subject on the right demonstrating the posterior and superior prepondefance of the terminal QRS loop.

ward (counterclockwise) rotation of the mean QRS vector or the appearance of the qR pattern at V_3R or V_1 in the ordinary electrocardiogram.

It was pointed out by Parkinson and Hogle[20] that the outflow tract of the right ventricle initially shows the most marked change in muscular hypertrophy. Gardberg and Ashman[21] in describing the spread of the excitation phase showed that the outflow tract is the last portion of the right ventricle to be depolarized. This may explain why the early changes begin at the terminal portion of the QRS loop in patients with early right ventricular hypertrophy.

Schaffer and Beinfeld[22] had described the changes in the spatial vectorcardiogram of infants as being identical with the previous description of right ventricular preponderance.

As Goldberger and Schwartz[23] have indicated, the differentiation of the early QRS complex changes from those resulting from alterations in position of the heart is an important consideration when dealing with patients with pulmonary emphysema. Some positional changes may well occur, but if all the changes were due to position one would expect the P- and T-wave mean vectors to shift proportionally to the mean QRS vector. This does not occur. Additional evidence that the changes are not all positional is well demonstrated by the wire loop models of the stereovectorcardiograms. These show the prominent terminal portion of the QRS loop that is directed posteriorly to the right and superiorly. This is best seen in the sagittal plane. This finding was not apparent in any of the control subjects.

If one supports the thesis that the electrocardiogram is the summation of an infinite number of individual vectors, it logically follows that preponderance to the right or left of the mean QRS vector depends upon the dominance of these infinite vector forces in one or the other direction. The magnitude, direction and sense of an electrical potential are dependent upon two factors: the muscle mass and a dynamic change in the ventricular muscle that occurs with changes in work. The former is self-evident from an electrocardiographic, clinical, and pathologic viewpoint. The dynamic physiologic muscular changes cannot be as clearly defined, but Kimura and Simonson[24] have shown shifts in the mean QRS vector that cannot be explained by anatomic positional changes in normal young men subjected to heavy exercise. This latter factor needs considerable clarification.

The changes in the average mean T-wave vectors indicate a more vertical position in the frontal plane and some forward rotation in the horizontal plane. There were considerable scatter and overlap in these data. Because of the small number of subjects no definite conclusion could be drawn. However, the lack of differentiation of the mean T vectors between the controls and the patients contrasts to the definite differentiation of the QRS vector. This is strong evidence that the QRS changes are not on the basis of anatomic positional changes and precede the changes of the T vector which is of importance for early diagnosis of right ventricular preponderance.

Large peaked P waves, "P pulmonale," have been classically associated with pulmonary emphysema. Recently reports have described peaked P waves in normal patients with vertical hearts.[25] In the frontal plane the data presented

show a trend to a more vertical mean P-wave vector. The magnitude of the P-wave vector in space could not be determined, and this should be done in order to determine that the classical interpretation of auricular hypertrophy as the cause of the peaked P waves is valid. The lack of correlation between this finding and clinical cor pulmonale would suggest that the finding is not related to auricular hypertrophy.

The data presented indicate that there is a gradual development of right ventricular preponderance in patients with chronic pulmonary emphysema. Special techniques such as concentric precordial leads and spatial vectorcardiography were employed to bring out these changes. In the light of these findings some deductions can be made from the usual twelve lead electrocardiograms. These are as follows:

1. All patients with right ventricular preponderance had a mean QRS frontal plane vector (axis) of greater than +95 degrees.

2. Shift of the transitional complexes to or beyond V_6 together with right axis deviation was uniformly seen in the earlier cases.

3. The appearance of a qR pattern together with the above findings in V_3R or V_1 was noted in the more marked cases.

4. The appearance of S_1, S_2, S_3 in the limb leads is seen in the cases with right ventricular preponderance due to the posterior direction of the mean QRS vector. This was noted in four of the five cases with right ventricular preponderance.

Any one of the above findings alone is not diagnostic but a combination of the right axis deviation together with the QRS changes as noted is highly suggestive of early right ventricular preponderance.

SUMMARY

1. A group of sixteen subjects with severe pulmonary emphysema was studied.

2. Thirty-four precordial and six limb leads were taken in each of these subjects and a control group.

3. Stereovectorcardiograms were obtained in twelve of the subjects with chronic pulmonary emphysema. Stereovectorcardiograms were also obtained in the control subjects.

4. The subjects exhibited a transition from no electrocardiographic evidence of right ventricular preponderance to right ventricular strain. This transition of changes was discussed and the changes of early right ventricular preponderance were stressed as was the application of the routine electrocardiogram.

REFERENCES

1. Kahn, M. H.: The Electrocardiogram in Bronchial Asthma, Am. J. M. Sc. **173**:555, 1927.
2. Winternitz, M.: Zur Pathologie des Menschlichen Vorhofelektrokardiogramms, Med. Klin. **31**:1575, 1935.
3. Grant, R. P.: The Relationship of Unipolar Chest Leads to the Electrical Field of the Heart, Circulation **1**:878, 1950.
4. Simonson, E.: The Distribution of Cardiac Potentials Around the Chest in One Hundred and Three Normal Men, Circulation **6**:201, 1952.

5. Schmitt, O. H., and Levine, R. B.: Direct Visual Examination of Stereovectorelectrocardiograms, Federation Proc. **11**:140, 1952.
6. Schmitt, O. H.: Cathode-Ray Presentation of Three-Dimensional Data, J. Appl. Physics **18**:819, 1947.
7. Keys, A., Brozek, J., Henschel, A., Mickelsen, O., and Taylor, H. L.: The Biology of Human Starvation, Minneapolis, 1950, University of Minnesota Press, Vol. I, pp. 198-208.
8. Hellerstein, H. K., and Santiago-Stevenson, D.: Atrophy of the Heart: A Correlative Study of Eighty-Five Proved Cases, Circulation **1**:93, 1950.
9. Higgins, G. K.: Effect of Pulmonary Tuberculosis Upon the Weight of the Heart, Am. Rev. Tuberc. **49**:255, 1944.
10. Barnes, A. R., and Whitten, M. B.: Study of T Waves Negativity in Predominant Ventricular Strain, AM. HEART J. **5**:14, 1929.
11. Wilson, F. N., Johnston, F. D., Rosenbaum, F. F., Erlanger, H., Kossmann, C. E., Hecht, H., Cotrim, N., Menezes de Oliviera, R., Scarsi, R., and Barker, P. S.: The Precordial Electrocardiogram, AM. HEART J. **27**:19, 1944.
12. Myers, G. B., Klein, H. A., and Stofer, B. E.: The Electrocardiographic Diagnosis of Right Ventricular Hypertrophy, AM. HEART J. **35**:1, 1948.
13. Myers, G. B.: The Form of the QRS Complex in the Normal Precordial Electrocardiogram and in Ventricular Hypertrophy, AM. HEART J. **39**:637, 1950.
14. Sokolow, M., and Edgar, A. L.: A Study of the V Leads in Congenital Heart Disease, AM. HEART J. **40**:232, 1950.
15. Rosenman, R. H., Silber, E., and Katz, L. N.: The Value of the aV Limb Leads and the V Chest Leads V_{4R} to V_7 in Routine Clinical Electrocardiography, AM. HEART J. **40**:573, 1950.
16. Oglesby, P., Myers, G. S., and Campbell, J. A.: The Electrocardiogram in Congenital Heart Disease, Circulation **3**:564, 1951.
17. Johnson, J. B., Ferrer, M. I., West, J. R., and Cournand, A.: The Relation Between Electrocardiographic Evidence of Right Ventricular Hypertrophy and Pulmonary Arterial Pressure in Patients With Chronic Pulmonary Disease, Circulation **1**:536, 1950.
18. Lasser, R. P., Borun, E. R., and Grishman, A.: Spatial Vectorcardiography: Right Ventricular Hypertrophy as Seen in Congenital Heart Disease. VII, AM. HEART J. **42**:370, 1951.
19. Kimura, N.: Three Dimensional Vectorcardiography. Read Before the Thirteenth Annual Scientific Session of the Japanese Association of Angio-Cardiology, Kyoto, Japan, March 30, 1949.
20. Parkinson, J., and Hogle, C.: The Heart in Emphysema, Quart. J. Med. **6**:59, 1937.
21. Gardberg, M., and Ashman, R.: The QRS Complex of the Electrocardiogram, Arch. Int. Med. **72**:210, 1943.
22. Schaffer, A. I., and Beinfeld, W. H.: The Vectorcardiogram of the Newborn Infant, AM. HEART J. **44**:89, 1952.
23. Goldberger, E., and Schwartz, S. P.: Electrocardiograms in Chronic Pulmonary Disease—A Theoretical Interpretation, Am. Rev. Tubere. **53**:34, 1946.
24. Kimura, N., and Simonson, E.: Unpublished data.
25. Zollner, S.: The Recognition of Right Heart Strain With Special Reference to Pulmonary Emphysema and Value of the So-Called P-Pulmonale, Arch. Kreislaufforsch, **14**:353, 1949.

THE EFFECT OF LITHIUM CHLORIDE ON THE ELECTROCARDIOGRAM OF THE ISOLATED PERFUSED HEART*

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THE primary purpose of this study was to analyze the changes in the electrocardiogram of the isolated perfused hearts of the turtle and of the dog which attend the addition of lithium chloride to the perfusate. Similarly, the effects of lithium chloride were investigated on hearts first subjected to either an excess or a deficiency of potassium, calcium, or sodium in the perfusate.

PROCEDURE

The hearts were prepared and perfused in the manner described in a previous publication.[1] Electrodes were placed within the cavity of the ventricle and against the epicardium of the ventricle (left ventricle of the dog heart). The two electrodes were attached to the leads of a "Sanborn tribeam stethocardiette," so that action potentials from the cavity and the surface of the left ventricle were recorded simultaneously. By means of a rubber membrane tambour and a transducer the mechanical activity of the turtle ventricle was frequently recorded on the same record as the action potential from the cavity of the ventricle.

RESULTS

1. The Electrocardiographic Changes Produced by the Presence of Lithium Chloride in the Perfusate.—After control records had been established, lithium chloride was added to the perfusate in concentrations ranging from 1 to 8 Gm. per liter (25.72 to 205.76 meq. lithium per liter), and the electrocardiographic changes were analyzed.

A concentration of 25.72 meq. of lithium per liter of perfusate produced no change in the electrocardiogram. In the presence of 51.44 meq. of lithium per liter the changes in the tracings from both the cavity and epicardial leads were limited to a slight decrease in heart rate, a decrease in the amplitude of the QRS complex, and a slight increase in the duration of the S-T interval by virtue of both a prolonged S-T interval and a broad T wave (Figs. 1 and 2).

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When the concentration of lithium in the perfusate was increased to 102.88 meq. or more per liter there was a further decrease in ventricular rate accompanied by an increase in the S-T interval and in width of the T wave (Fig. 2). The QRS interval was unaltered.

With increasing concentrations of lithium in the perfusate of the turtle heart the duration of the mechanical contraction increased but the force of contraction decreased, as manifested by a decrease in the amplitude of the wave of contraction. Ventricular arrest in diastole, but not in a markedly dilated state, finally developed. The concentration of lithium in the perfusate that produced ven-

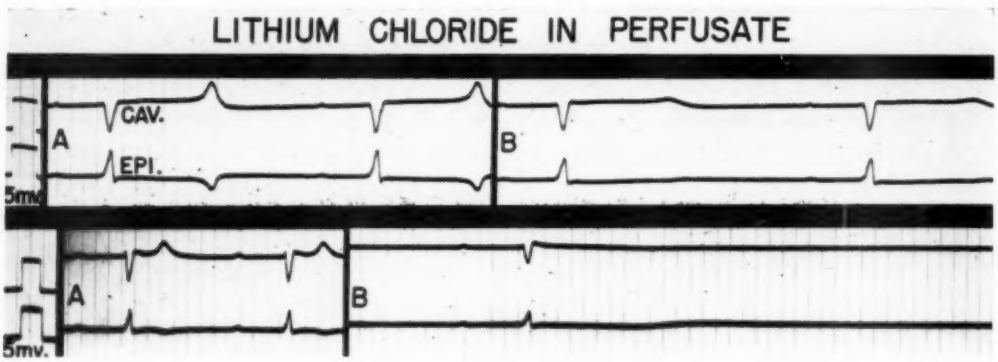

Fig. 1.—The electrocardiographic effects of lithium chloride on the isolated turtle heart. *CAV.* = Electrocardiogram from electrode in the ventricular cavity. *EPI* = Electrocardiogram from electrode on the epicardial surface of the ventricle.

First row. *A.* Control. *B.* After one hour of perfusion with a solution containing 51.44 meq. lithium per liter.

Second row. *A.* Control. *B.* After thirty-five minutes of perfusion with a solution containing 205.76 meq. lithium per liter.

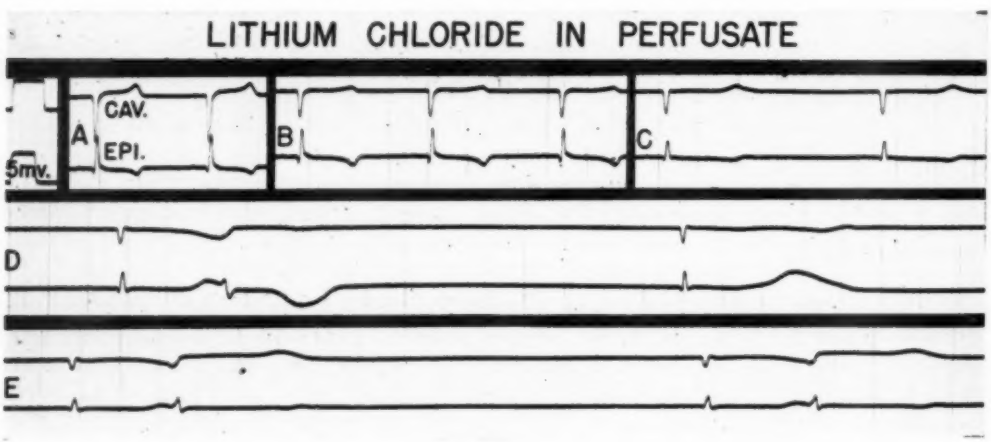

Fig. 2.—The electrocardiographic effects of adding lithium chloride to the perfusate of an isolated dog heart. *CAV.* = Electrocardiogram from electrode in the cavity of the left ventricle. *EPI* = Electrocardiogram from electrode on the epicardial surface of the left ventricle.

A. Control. *B.* After eight minutes of perfusion with a solution (Tyrode's) containing 51.44 meq. lithium per liter. *C.* After ten minutes of perfusion with a solution containing 102.88 meq. lithium per liter. *D.* and *E.* After five minutes and ten minutes respectively of perfusion with a solution containing 154.32 meq. lithium per liter.

tricular arrest varied between 102.9 and 205.8 meq. per liter. After complete cessation of mechanical and electrical activity, contraction of the turtle ventricle could be induced easily by both mechanical and electrical stimulation (Harvard inductorium). Stimulation and subsequent contraction of either the sinus venosus or the atria also initiated both electrical and mechanical ventricular systole. (Mechanical activity was not recorded in the experiments on the dog heart.)

2. Electrocardiographic Changes Produced by Adding Lithium Chloride to a Perfusate Containing an Excess of Potassium.—Hearts were perfused with a perfusate containing a concentration of potassium sufficient to produce the electrocardiographic changes characteristic of potassium excess. These changes consisted of a prolonged QRS interval, a shortened S-T interval, an increase in amplitude of the T wave and terminally the development of monophasic or diphasic complexes without a clear separation of the various components of electrical activity.[1] Lithium (as lithium chloride) was then added to the perfusate in a concentration of 25.72 or 51.44 meq. per liter.

In the turtle heart the addition of lithium to the perfusate containing an excess of potassium increased the force of contraction and the duration of mechanical systole of the ventricle and further reduced the ventricular rate (Fig. 3). However, the ventricular rate of the dog heart was unaffected by the addition of lithium unless complete ventricular arrest had been produced by potassium excess alone. Then the addition of lithium restored the heart beat to a rate about equal to that before cardiac arrest occurred.

The prolonged QRS interval, characteristic of an excess of potassium, was shortened when lithium was added (Fig. 3).

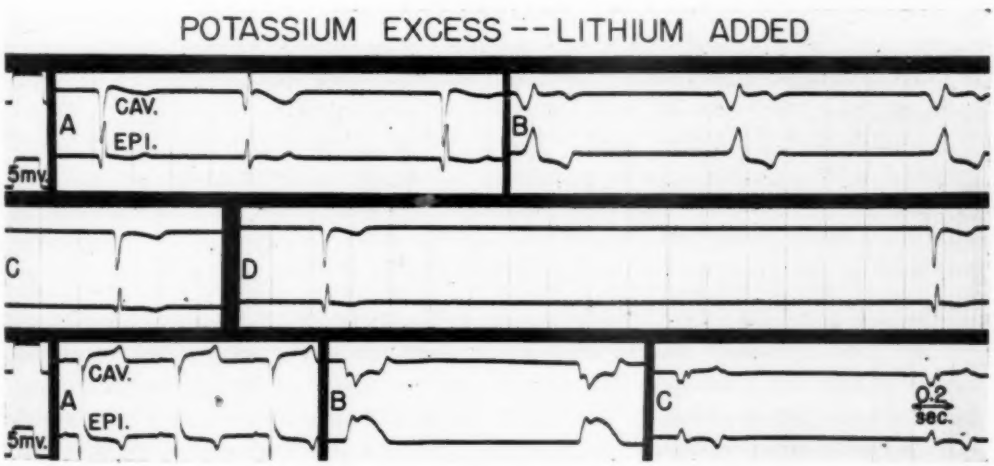

Fig. 3.—The electrocardiographic changes produced by adding lithium chloride to a perfusate containing an excess of potassium.

First two rows. *A.* Control (second complex is abnormal). *B.* After ten minutes of perfusion with a solution containing an excess of potassium (12.02 meq. per liter). *C.* and *D.* After two and thirty minutes respectively of perfusion with a solution containing 12.02 meq. potassium per liter plus 25.72 meq. lithium per liter. Ventricular rate was irregular at thirty minutes (*D*).

Last row. *A.* Control. *B.* After three minutes of perfusion with a solution containing 12.02 meq. potassium per liter (transient arrest after one and one-half minutes). *C.* After four minutes of perfusion with a solution containing 12.02 meq. potassium per liter and 51.44 meq. lithium per liter.

The short S-T interval, caused by an excess of potassium, was increased in the records of both the turtle and dog hearts. The addition of lithium broadened the T waves.

If the advanced changes of an excess of potassium were such that the components of electrical activity were inseparable, consisting of monophasic and diphasic forms, the addition of lithium restored the various components of electrical activity (Fig. 3).

3. The Electrocardiographic Effects of Adding Lithium Chloride to a Potassium-free Perfusate.—Hearts were perfused with a potassium-free perfusate until the electrocardiographic changes characteristic of a potassium deficiency developed.[1] These changes consisted of a prolonged P-R interval, prolonged QRS interval, prolonged after-potentials with increased duration of electrical activity in the turtle heart. Except for slight or no widening of the QRS complex before atrioventricular dissociation developed, similar changes took place in the dog heart. Finally lithium (51.44 meq. per liter) was added to the perfusate.

Following the addition of lithium chloride there was a decrease in ventricular rate and a decrease in the amplitude of the QRS complex. The prolonged QRS interval characteristic of potassium deficiency in the turtle heart was markedly shortened. The QRS interval remained the same in the records from the dog heart.

With the decrease in rate after the addition of lithium the S-T and U intervals were further prolonged, and the width of the T wave seemed increased.

When partial atrioventricular dissociation, ventricular fibrillary bursts, or actual ventricular fibrillation developed during the perfusion of the turtle heart with a potassium-free perfusate, the addition of lithium resulted in a cessation of both the fibrillary bursts and the ventricular fibrillation, and the atrioventricular conduction was restored within one minute. The rate of the heart, however, became even slower and more irregular. Mechanically, the addition of lithium increased the force and duration of systolic contraction.

Ventricular fibrillation, which invariably occurred when dog hearts were perfused with a potassium-free perfusate, did not develop when the potassium-free perfusate contained 51.44 meq. of lithium per liter. However, in contrast to what occurred with the turtle heart the addition of lithium to the potassium-free perfusate in the presence of ventricular fibrillation did not stop the fibrillation when this was once established.

4. The Effects of Adding Lithium Chloride to a Perfusate Containing an Excess of Calcium Chloride.—Hearts were perfused with a perfusate containing an excess of calcium chloride. In the turtle heart perfusate the calcium content was increased from 5.46 to 21.84 meq. per liter; in the dog heart perfusate the calcium content was increased from 3.60 to 14.4 or 21.6 meq. per liter. After the development of electrocardiographic changes attributed to the excess of calcium, lithium (51.44 meq. per liter) was added to the perfusate.

An excess of calcium in the perfusate produced the following changes:

a. There was an increase in the force of contraction and in the duration of mechanical systole of the turtle heart with little change in rate.

b. The P-R interval increased. Partial or complete atrioventricular dissociation developed in the experiments on the dog heart in which the concentration of calcium was 21.6 meq. per liter of perfusate (Fig. 4).

c. The QRS interval was prolonged. In the dog heart the QRS interval was increased, but only a minimal increase was noted before atrioventricular dissociation developed.

d. The width of the T waves increased. The T waves became flat or isoelectric in the records of the turtle heart, but in those of the dog heart the amplitude of the T waves was usually increased, although the beginning of the T wave was difficult to separate from the S-T segment.

e. Although in the turtle heart the S-T interval did not seem to be altered, accurate measurements of the S-T interval were impossible because of the flat or isoelectric T waves. In the dog heart tracings, an increase in the S-T interval was associated with the decrease in the ventricular rate which followed the development of atrioventricular dissociation.

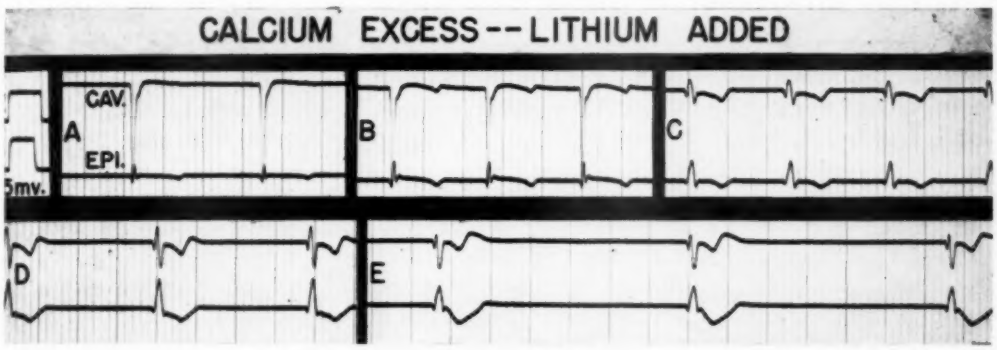

Fig. 4.—The electrocardiographic changes produced by the addition of lithium chloride to a perfusate containing an excess of calcium. *CAV.* = Electrocardiogram from electrode in cavity of left ventricle. *EPI.* = Electrocardiogram from electrode on epicardial surface of left ventricle.

A. Control. *B, C,* and *D.* After one minute, one and one-half minutes, and four minutes respectively of perfusion with a solution containing an excess of calcium (21.6 meq. per liter). *E.* After five minutes of perfusion with a solution containing 21.6 meq. calcium per liter and 51.44 meq. lithium per liter. (Lithium did not counteract the effects of the excess of calcium.)

f. In the turtle heart, the take-off of the S-T segment was consistently elevated in the tracings from the cavity lead and usually depressed in the tracings from the epicardial lead. In the dog heart, alterations in the elevation or depression of the S-T segments were variable.

In both dog and turtle hearts, the addition of lithium to the perfusate containing an excess of calcium decreased the amplitude of the QRS complex and slowed the ventricular rate slightly. In the turtle heart the addition of lithium also shortened the prolonged QRS interval and increased still more the force of contraction.

5. The Effects of Adding Lithium Chloride to a Calcium-free Perfusate.—Hearts were perfused with a solution which, except for the absence of calcium, contained the usual concentrations of the other electrolytes. After cessation of effective mechanical contractions the hearts were perfused with the standard

perfusate. Then the hearts were perfused with a calcium-free perfusate containing 51.44 meq. of lithium per liter.

In some experiments the hearts were first perfused with the calcium-free perfusate, and then lithium (25.72 or 51.44 meq. per liter) was added.

Perfusion with the calcium-free perfusate produced the following changes (Fig. 5):

a. The rate of the ventricle was slightly decreased.

b. The P-R interval was prolonged. With the decrease in rate, the S-T interval was prolonged and the width of the T wave increased.

c. The QRS interval remained the same. The amplitude of the QRS complex was decreased in the records of the turtle heart.

d. In the turtle heart, a progressive decrease in the force of contraction occurred, and finally there was almost complete cessation of recorded mechanical contractions with the ventricle in diastole. However, the electrical activity persisted unabated without change in the QRS interval.

In the dog heart, cessation of visible mechanical contraction was observed in all experiments within one and one-half to three minutes. Electrical activity, however, persisted for as long as perfusion with the calcium-free perfusate was continued (twenty minutes in one experiment). Changes in mechanical events were not recorded.

The addition of lithium chloride to the calcium-free perfusate did not reverse or prevent the electrocardiographic changes produced by the calcium deficiency.

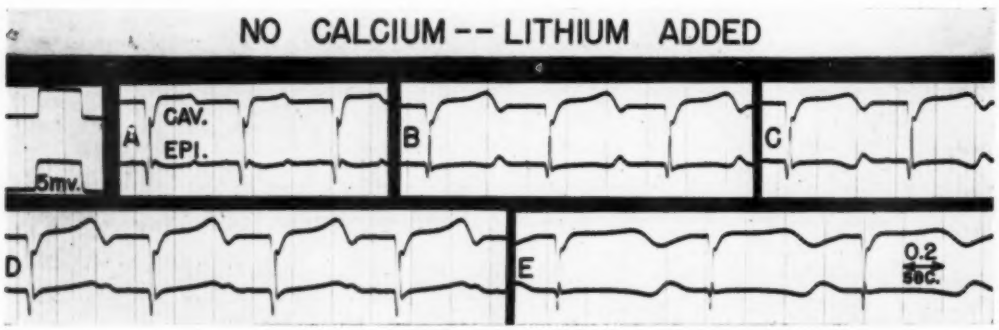

Fig. 5.—The electrocardiographic changes produced by the addition of lithium chloride to a calcium-free perfusate.

A. Control. *B*, *C*, and *D*. After one minute, one and one-half minutes, and two minutes respectively of perfusion with a calcium-free solution (cessation of visible mechanical activity at one and one-half minutes). *E*. After two minutes of perfusion with a calcium-free solution containing 51.44 meq. lithium per liter. (Lithium did not counteract the effects of the calcium deficiency.)

6. The Effects on the Electrocardiogram of Adding Lithium Chloride to a Perfusate Containing a Very Low Sodium Content.—Hearts were perfused with a very low sodium chloride concentration in the perfusate (only 4.4 meq. sodium per liter in the turtle heart perfusate and 12.32 meq. sodium per liter in the dog heart perfusate), for one to five minutes. Then lithium chloride (51.44 or 154.32 meq. lithium per liter) was added to the perfusate.

The following electrocardiographic changes developed during the very few minutes that the hearts were perfused with a very low sodium chloride concentration in the perfusate:

a. There was an increase in heart rate which was moderate in the turtle, but marked in the dog. The heart of the turtle was perfused for ten minutes in one experiment which resulted in ventricular arrest, but the P waves persisted. In experiments on the dog heart the P waves disappeared early and ventricular fibrillation developed within three or four minutes of perfusion with the sodium chloride-free perfusate.

b. Both the QRS interval and amplitude of the QRS complex increased. However, in the dog heart the complexes were bizarre after the disappearance of the P waves.

c. Associated with the increase in cardiac rate there was shortening of the S-T interval.

d. The S-T segment changes were extreme. There were a marked segmental elevation shown in the tracings from the cavity lead and a marked depression in the records from the epicardial lead.

e. The T waves were broad.

The addition of lithium was ineffective in reversing the electrocardiographic changes caused by marked sodium deficiency and did not prevent the development of ventricular fibrillation in the dog heart. In the turtle heart the addition of 154.32 meq. of lithium per liter decreased the ventricular rate after an initial transient period of ventricular arrest. With the decrease in rate, the P-R interval and the S-T interval were prolonged. The amplitude of the QRS complex was decreased. The segmental changes, though still present, were less marked.

In another set of experiments hearts were perfused with a perfusate in which the content of sodium was decreased from 146.0 to 75.15 meq. per liter in the turtle heart perfusate and from 149.0 to 80.70 meq. per liter in the dog heart perfusate. After several minutes, during which the changes in the electrocardiogram attributed to a low sodium concentration developed, lithium chloride (lithium 51.44 or 205.76 meq. per liter) was added to the perfusate.

In the turtle heart, the addition of lithium (51.44 meq. per liter) to the perfusate slightly shortened the prolonged QRS interval, and the segmental changes became less marked.

In the dog heart, after the addition of lithium, the P waves which had disappeared returned and regular atrioventricular rhythm was re-established within two to three minutes with a rate about equal to the control cardiac rate which was from 70 to 120 beats per minute in two of the three records. In the third record the P waves did not return but the ventricular rate increased again to the control rate or from 50 to 100 beats per minute. With the restoration of regular sinus rhythm, the prolonged QRS interval was shortened, the potential of the QRS complex was slightly decreased, and there was a slight lengthening of the S-T interval.

Also in the dog heart, the marked segmental changes characteristic of low sodium in the perfusate, if present, became less marked with the addition of lithium.

COMMENT

In 1949 and 1950 several reports[2-8] appeared in the literature of cases of suspected lithium intoxication. Electrocardiograms were reported in two instances. Hanlon and associates[4] noted no changes in the electrocardiogram of one case in spite of a high lithium blood level, although in another tracing taken as the lithium blood level was decreasing a transient intraventricular heart block was noted. In another report Stern[6] noted bradycardia and more prominent T waves in one case. The serum potassium was elevated in this case.

Good (1903)[9] reviewed the older literature on lithium and gave credit to Hesse in 1875 for first observing that lithium chloride, when injected into a vein of frogs, rabbits, and doves, caused cardiac arrest in diastole. Good also referred to the work of Krumhoff (1884) who found that when a lithium salt was injected into the blood of an animal it depressed the heart's action, caused a decrease in blood pressure, and in large doses stopped the heart in diastole.

Foulks and associates[10] noted increased renal excretion rates of potassium after the intravenous infusion of lithium in dogs.

McKusick[11] administered isotonic lithium chloride solution intravenously to dogs, cats, and rabbits, and intraperitoneally to guinea pigs; Radomski and associates[12] gave dogs lithium chloride solutions orally. Both workers reported elevated blood potassium levels as well as blood lithium levels and noted electrocardiographic changes similar to those produced by potassium intoxication in dogs.[13] Radomski and associates[12] produced plasma lithium concentrations within the toxic range without elevating the serum potassium by injecting lithium chloride intraperitoneally in dogs and found no electrocardiographic changes. They, therefore, concluded that the electrocardiographic changes which developed after the oral or intravenous administration of lithium chloride were due to hyperpotassemia and not to lithium.

In the present study a high concentration of lithium in the perfusate decreased the heart rate; with the decrease in rate, the phase of repolarization (S-T interval) was prolonged. Although the voltage of the QRS complex was decreased, there was no delay in depolarization of the ventricle (QRS interval). The terminal event in the turtle heart was atrial and ventricular arrest in diastole but not in a markedly dilated state. It should be emphasized that the concentration of lithium necessary to produce electrocardiographic changes in our experiments greatly exceeded the lithium blood levels noted in cases of human lithium intoxication and in dogs following intravenous, oral, or intraperitoneal injections of lithium chloride.[11,12]

SUMMARY

Action potentials were recorded simultaneously from the cavity and the epicardium of the ventricle of the isolated perfused heart of the dog and the turtle before and after alteration of the concentrations of the various cations in the perfusate.

High concentrations of lithium chloride in the perfusate slowed the cardiac rate, prolonged the S-T interval, and broadened the T waves. The width and contour of the QRS complex were unaltered, but the voltage was decreased. A

very high concentration of lithium seemed to affect primarily the automaticity of the turtle heart. Lithium in a concentration of 25.72 meq. per liter or greater counteracted many of the electrocardiographic effects of an excess of potassium; more specifically, lithium shortened the delayed intraventricular conduction time, increased the shortened S-T interval, and again separated the components of electrical activity from the terminal monophasic and diphasic forms of potassium intoxication.

Lithium could not substitute for calcium or sodium in the perfusing solution, although lithium tended to counteract the electrocardiographic effects of a moderately low sodium concentration in the perfusate.

An excess of calcium in the perfusate caused an increase in the QRS interval, widening of the T wave, a slight increase in the amplitude of the S wave in the epicardial tracing, and atrioventricular dissociation. The absence of calcium from the perfusate prolonged the P-R interval and Q-T interval, without change in the width or contour of the QRS complex, and broadened the T waves.

REFERENCES

1. Butcher, W. A., Wakim, K. G., Essex, H. E., Pruitt, R. D., and Burchell, H. B.: The Effect of Changes in Concentrations of Cations on the Electrocardiogram of the Isolated Perfused Heart, Am. Heart J. **43**:801-814, 1952.
2. Corcoran, A. C., Taylor, R. D., and Page, I. H.: Lithium Poisoning From the Use of Salt Substitutes, J. A. M. A. **139**:685-688, 1949.
3. Greenfield, Irving, Zuger, Max, Bleak, R. M., and Bakal, Sandra F.: Lithium Chloride Intoxication, New York State J. Med. **50**:459-460, 1950.
4. Hanlon, L. W., Romaine, Mason, III, Gilroy, F. J., and Deitrick, J. E.: Lithium Chloride as a Substitute for Sodium Chloride in the Diet; Observations on Its Toxicity, J. A. M. A. **139**:688-692, 1949.
5. Peters, H. A.: Lithium Intoxication Producing Chorea Athetosis With Recovery, Wisconsin M. J. **48**:1075-1076, 1949.
6. Stern, R. L.: Severe Lithium Chloride Poisoning With Complete Recovery: Report of Case, J. A. M. A. **139**:710-711, 1949.
7. Talbott, J. H.: Use of Lithium Salts as a Substitute for Sodium Chloride, Arch. Int. Med. **85**:1-10, 1950.
8. Waldron, A. M.: Lithium Intoxication Occurring With the Use of a Table Salt Substitute in the Low Sodium Dietary Treatment of Hypertension and Congestive Heart Failure, Univ. Hosp. Bull., Ann Arbor, **15**:9-10, 1949.
9. Good, C. A.: An Experimental Study of Lithium, Am. J. M. Sc. **125**:273-284, 1903.
10. Foulks, J. C., Mudge, G. H., and Gilman, Alfred: Effect of Lithium on the Renal Excretion of Potassium, Federation Proc. **9**:41-42, 1950.
11. McKusick, V. A.: Effect of Lithium on the Electrocardiogram of Animals, Federation Proc. **9**:84, 1950.
12. Radomski, J. L., Fuyat, H. N., Nelson, A. A., and Smith, P. K.: The Toxic Effects, Excretion, and Distribution of Lithium Chloride, J. Pharmacol. & Exper. Therap. **100**: 429-444, 1950.
13. Winkler, A. W., Hoff, H. E., and Smith, P. K.: Electrocardiographic Changes and Concentration of Potassium in Serum Following Intravenous Injection of Potassium Chloride, Am. J. Physiol. **124**:478-483, 1938.

FURTHER OBSERVATIONS ON "SUSTAINED" HYPERTENSION IN THE RAT

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THE possibility that the adrenal cortex participates in certain forms of essential hypertension has stimulated a considerable amount of investigation. Particular impetus was given these studies by the demonstration that desoxycorticosterone acetate (DCA) could produce a hypertensive response in a wide variety of species.[1,2] If a DCA-like material were involved in essential hypertension, however, it would be expected that abnormalities in sodium and/or potassium metabolism would be readily discernible in at least some patients afflicted with the disease. Disappointingly few patients, however, show anything like the clear-cut disturbance which would have been expected by this view.[3] Our recent work with Compound F acetate (17-OH-corticosterone-21-acetate) may provide a partial explanation of this finding, for while this agent is sufficiently DCA-like to produce an even more marked hypertension than DCA in our hands, it nonetheless does not produce the marked electrolyte imbalance of that synthetic steroid.[4] Since Compound F is not only naturally occurring but may even be one of the major adrenal steroids,[5] it is of obvious importance to determine whether the hypothesis implicating a "DCA-like material" in some cases of essential hypertension would permit the substitution of the more specific agent, Compound F.

Although Turner and Grollman[6] have shown that the hypertension which follows bilateral nephrectomy does not require the presence of the adrenal, this can hardly be considered to negate the idea of adrenal participation in essential hypertension. No one would be so rash as to consider that all essential hypertension is of one etiology or that all forms of experimental hypertension are the same.

A further objection to an adrenal implication in essential hypertension has been the failure to demonstrate unequivocal evidence of adrenal hyperfunction except in such specific instances of endocrine imbalance as Cushing's syndrome. We[7,8] have recently proposed, as a working hypothesis, an adrenal-renal imbalance. According to this view hypertension could arise either by hyperfunction of the adrenal on the one hand or by an impairment of the renal mechanism for handling the hypothetical adrenal pressor material on the other. Based on this

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view, we have shown that animals subjected to intensive treatment with DCA in some cases remain permanently hypertensive after treatment is discontinued. Tentatively, since no renal anatomic fault can be held accountable for the persistent hypertension, we have suggested that the kidney's ability to handle the "adrenal pressor material" has been impaired by overtreatment with DCA. It is obviously important to establish whether this effect of DCA can be duplicated by Compound F, and experiments are now in progress to investigate this point.

In previous work with the post-DCA "sustained" hypertension we have been unable to find any concrete basis for the disease and have suggested that, accordingly, by definition, it would seem to be "essential." The present report is concerned with further work aimed at determining whether any objective evidence of renal damage can be demonstrated. So far, we are still unable to find such evidence.

EXPERIMENTAL PROCEDURE

Sixty male albino rats of an inbred Wistar strain, weighing approximately 100 grams, were divided into three groups. The first group, consisting of ten animals, served as untreated controls, while the remaining fifty animals were subjected to a unilateral nephrectomy. Of these, ten animals served without further treatment as the uninephrectomized control Group 2. The forty animals of Group 3 were subjected to a period of intensive treatment with DCA together with the partial substitution of 1 per cent saline as drinking water. DCA was administered as follows: one week after uninephrectomy two pellets (¼ of a 75 mg. Cortate pellet each) were implanted subcutaneously and one pellet was implanted every four days thereafter until a total of seven pellets had been implanted in three weeks. Forty days after the initiation of DCA administration, treatment was stopped and the implanted pellets were surgically recovered. Saline was substituted for tap water only from the seventh to the twenty-second day of treatment.

At the conclusion of treatment the animals were observed without further interference for sixteen weeks except for an occasional indirect blood pressure recording. The present report is concerned with studies carried out at the end of the period of observation. At this time, the glomerular filtration rate using inulin as test substance[9] was determined. Simultaneously, the plasma sodium and potassium were determined as well as the excretion of these substances in the urine. One week after the completion of these tests, blood pressure was determined directly from the aorta using a Sanborn Electromanometer. This procedure has been discussed elsewhere.[10] The animals were killed immediately after the blood pressure recording and hearts, kidneys, and adrenals fixed for further study.

OBSERVATIONS

The final experimental procedures, because of their time-consuming and complex nature, were restricted to a study of eight animals from Group 1, eight from Group 2, and twenty animals taken at random from Group 3. The pertinent blood pressure observations are summarized in Table I. As we have previously observed, indirect blood pressure determinations in our hands are a reliable

indication of the trend of the blood pressure in comparable groups. The actual value obtained apparently does not represent either systolic, diastolic, or mean pressure.

At the time of cessation of DCA treatment the indirect blood pressure was markedly elevated, indicating that treatment was even more severe than that which we have previously reported. Sixteen weeks after all treatment had been stopped, indirect blood pressure determinations still showed a significant hypertension to be present in Group 3 although the average was now somewhat lower. The animals of this group were, however, readily separable into one subgroup of animals whose blood pressure had clearly reverted to normal and another whose blood pressure had remained elevated. This subdivision was confirmed by direct manometry and agrees well with our previous observation that sustained hypertension follows DCA treatment only in some animals. Previously, with less intensive treatment about one-third of our animals had remained permanently hypertensive. In the present experiment we had purposely used a more severe and protracted DCA treatment period so that about two-thirds of the animals remained hypertensive, providing a better opportunity of studying the relation of the kidney and adrenal to the hypertensive process.

Relation of Blood Pressure to Organ Weight.—The following analysis of data was aimed at determining to what extent the kidneys might be involved in the sustained hypertensive process. Accordingly, only those animals from which complete data were available were included in the compilation. Complete data were available for six untreated controls, seven uninephrectomized controls, four post-DCA normotensives, and nine post-DCA hypertensives. The first set of data on these animals is presented in Table II.

Blood pressure was markedly elevated in the hypertensive group. This was true of systolic, diastolic, mean, and pulse pressures. Kidney weight was not increased in the normotensive post-DCA group and only moderately (not significantly) increased in the hypertensive group when compared with the untreated one-kidney animals of Group 2. An increase in heart weight was observed in both post-DCA groups but this was significant only in the hypertensive group. Adrenal weight was increased both absolutely and relative to surface area in both post-DCA groups so that apparently this factor also gives little clew as to the cause of difference between these two groups.

Renal Function and Sodium Handling.—The fundamental data concerning the same animals shown in Table II are presented in Table III. A significant diminution in the glomerular filtration rate as determined with inulin occurred in both of the groups which had previously been under DCA treatment so that this impairment in glomerular function cannot be held accountable for the persistence of hypertension in some animals.

Despite the impaired glomerular filtration rate, plasma sodium remained at normal levels in the post-DCA groups. Further, the amount of sodium excreted during the clearance period was closely similar in all groups. Since the amount of sodium filtered was obviously reduced in the post-DCA groups, the only ex-

TABLE I

GROUP	BLOOD PRESSURE mm.Hg								
	AT END OF TREATMENT		16 WEEKS AFTER END OF TREATMENT						
	INDIRECT		INDIRECT	DIRECT					
				SYSTOLIC		DIASTOLIC		MEAN	
Control (8)	121 ± 6		125 ± 7	138 ± 9		99 ± 8		118 ± 10	
Uninephrectomy (8)	118 ± 12		126 ± 24	138 ± 9		99 ± 11		116 ± 10	
DCA-treated (17) Uninephrectomy	170 ± 17	normotensive (5)	153 127 ± 16	170 143 ± 13		121 100 ± 5		147 123 ± 6	
		hypertensive (12)	172 ± 17	181 ± 13		131 ± 11		157 ± 10	

$$\text{Standard Deviation} = \sqrt{\frac{\Sigma(x - \bar{x})^2}{n - 1}}$$

TABLE II

GROUP	BLOOD PRESSURE mm.Hg				KIDNEY WT. mg./100 cm.²	HEART WT. mg./100 cm.²	ADRENAL WT. mg./100 cm.²	ADRENAL WT. mg.
	SYSTOLIC	DIASTOLIC	MEAN	PULSE				
Control	140 ± 8	101 ± 9	121 ± 11	39 ± 5	390 ± 39	275 ± 24	10.5 ± 1.9	65.7 ± 11.4
Uninephrectomy	138 ± 9	99 ± 12	115 ± 11	39 ± 3	298 ± 54	256 ± 42	10.0 ± 1.5	63.7 ± 9.9
Uninephrectomy + DCA Post-DCA normotensive	140 ± 12	99 ± 7	121 ± 7	41 ± 8	318 ± 44	294 ± 43	12.4 ± 1.6	73.3 ± 6.2
Uninephrectomy + DCA Post-DCA hypertensive	185 ± 13	132 ± 12	160 ± 10	53 ± 7	369 ± 84	314 ± 23	11.9 ± 1.6	71.6 ± 7.9

planation for the normal excretion seems to be that in these groups the tubular reabsorption of sodium was somewhat diminished. A very small reduction in the tubular reabsorption of sodium would, of course, suffice to compensate for the diminished filtration of the ion, and this apparently is the case. Finer techniques than can be used in the rat would be necessary to fully elucidate the exact mechanism involved.

For the purposes of the present examination, however, it seems clear that the mechanisms maintaining a post-DCA hypertensive state are related neither to the glomerular filtration rate nor to the renal mechanisms for handling sodium.

Renal Function and Potassium Handling.—The fundamental data, again from the same animals which appeared in the two preceding tables, are shown in Table IV. The plasma level of potassium in the two post-DCA groups was again within the normal range in comparison with the uninephrectomized controls of Group II, although interestingly enough plasma potassium was somewhat elevated in all three one-kidney groups.

Despite a diminution in the amount of potassium filtered as a result of the impaired glomerular filtration rate in the post-DCA groups, the amount of potassium excreted was somewhat elevated in these groups. This might be due to either diminished reabsorption of filtered potassium or active tubular secretion of the ion. In four animals the amount excreted exceeded the amount filtered, suggesting that tubular secretion of potassium can occur in the rat. It is not possible, however, with these data to decide on which factor is involved.

Certainly these data, for the purposes of the present study, throw no light on the mechanism of the sustained hypertensive process.

Renal and Adrenal Structure.—The data concerning the histologic appearance of kidney sections stained with our routine haemalum, phloxine, and saffron stain, and of adrenal sections stained with Sudan black are given in Table V.

The kidneys of both normotensive and hypertensive post-DCA groups showed clear evidence of renal damage which we have hitherto classed as "nephrosclerosis" in the rat. Minimal lesions consist of hyalinization of the glomerular tuft with a well-defined thickening of the basement membrane surrounding the glomerulus, a discernible degree of tubular dilatation, and increased thickening of the media of small arterioles. These lesions, which for convenience are classified as one-plus, are usually patchy in distribution. Moderate, or two-plus, lesions are those where glomerular hyalinization has progressed to the point of obliterating the glomerulus; tubular dilatation is prominent and casts are numerous. These lesions, together with the vascular change, while still patchy are widely distributed throughout the parenchyma. Marked, or three-plus, lesions, while the same in character as the foregoing, are generalized in distribution so that only rarely is normal kidney structure encountered.

As shown in Table V minimal lesions may be encountered even normally in older rats where the full load is placed on one remaining kidney. Moderate and marked lesions occurred in those animals subjected to DCA treatment. While in general the lesions were more severe in the hypertensive animals, six out of

TABLE III

GROUP	C_{IN} c.c./100 cm.²/min.	PLASMA Na mg./100 c.c.	Na EXCRETED mg./100 cm.²/min.	C_{Na} c.c./100 cm.²/min.	Na FILTERED mg./100 cm.²/min.	Na REABSORBED mg./100 cm.²/min.	Na REABSORBED / Na FILTERED (%)
Control	0.26±0.04	857±44	0.027±0.013	0.0032±0.0015	2.18±0.34	2.15±0.34	98.67±0.67
Uninephrectomy	0.24±0.04	909±67	0.026±0.010	0.0029±0.0013	2.25±0.42	2.22±0.42	98.77±0.69
Uninephrectomy + DCA (Post-DCA normotensive)	0.18±0.06	858±39	0.023±0.007	0.0027±0.0007	1.55±0.40	1.53±0.40	98.29±0.84
Uninephrectomy + DCA (Post-DCA hypertensive)	0.16±0.05	872±60	0.028±0.018	0.0027±0.0022	1.40±0.05	1.37±0.50	97.7 ±1.63

Plasma Na values are expressed in mg./100 c.c. to facilitate recalculation of derived data.
In = inulin.
C = clearance.

TABLE IV

GROUP	PLASMA K mg./100c.c.	K EXCRETED mg./100 cm.²/min.	C_K c.c./100 cm.²/min.	K FILTERED mg./100 cm.²/min.
Control	22.7 ± 3.5	0.022 ± 0.018	0.105 ± 0.087	0.058 ± 0.016
Uninephrectomy	29.2 ± 6.5	0.029 ± 0.018	0.110 ± 0.089	0.073 ± 0.021
Uninephrectomy + DCA (Post-DCA normotensive)	27.5 ± 5.2	0.050 ± 0.041	0.169 ± 0.106	0.048 ± 0.010
Uninephrectomy + DCA (Post-DCA hypertensive)	29.1 ± 6.9	0.036 ± 0.044	0.117 ± 0.107	0.045 ± 0.012

Plasma K values are expressed in mg./100 c.c. to facilitate recalculation of derived data.

TABLE V

GROUP	ANIMAL NO.	NEPHROSCLEROSIS	ADRENAL LIPIDS	
Control	1120–1	0	+++	
	1120–2	0	+++	
	1120–3	0		Average +++
	1121–1	0	+++	
	1121–2	0	+++	
	1122–1	0	++	
Uninephrectomy	1123–1	++	+++	
	1123–3	0	+++	
	1123–4	0	++	
	1124–2	0	+++	Average ++
	1125–1	+	+	
	1125–2	+	0	
	1125–3	+	0	
Uninephrectomy + DCA Post-DCA Normotensive	1128–1	++	0	
	1128–4	++	++	Average +
	1130–1	++	0	
	1132–2	+++	++	
Uninephrectomy + DCA Post-DCA Hypertensive	1126–2	++	+	
	1127–3	+++	++	
	1129–4	++	+	
	1130–2	++	+	
	1130–3	+++	++	Average +
	1131–4	+++	+	
	1132–3	+++	++	
	1134–3	+++	+	
	1135–2	+++	+	

nine showing three-plus or marked lesions, still the overlap was such that it is not possible to correlate kidney damage with the hypertension. For example, it is impossible to distinguish between the three hypertensive and the three normotensive animals with two-plus nephrosclerosis from an examination of the kidney sections. Accordingly, we must conclude that the persistence of hypertension following cessation of DCA treatment is not directly dependent on any readily discernible renal anatomic fault.

It should be mentioned parenthetically that kidney sections were treated with tetrazolium chloride according to the method of Zweifach and associates.[11] The precipitate formed in all cases was needlelike, again providing no morphologic differentiating point between hypertensive and normotensive animals.

No gross histologic changes were observed in the adrenals of any animals in this series. Adrenal lipids, as demonstrated by the use of Sudan black, were reduced in both the hypertensive and normotensive post-DCA groups.

DISCUSSION

As we have already described, a sustained elevation in blood pressure may be induced in the rat by a short period of DCA treatment provided that treatment is sufficiently intense in the first instance to induce a well-marked hypertension. In the present experiment sustained hypertension developed in two-thirds of the animals originally treated with the steroid.

So far we have been unable to find the causal factor or factors in this "sustained" hypertension. Since, in line with our previous observations, renal lesions of the same type may occur in post-DCA treated animals regardless of whether the hypertension continues or abates, obviously these lesions cannot be held accountable. Indeed, the pattern of severity observed favors the view that, if there is any relation to renal damage in this condition it is that continued hypertension may aggravate the existing renal damage.

Functional studies are in the same vein, for a reduction in glomerular filtration rate occurred in the treated animals regardless of the blood pressure level. This reduction in glomerular filtration rate obviously resulted in a diminished filtered load of both sodium and potassium, but the kidney seems to have adapted to this so as to maintain normal plasma levels of these ions. The importance of these findings is that, contrary to the suggestion made by Braun-Menendez and associates[12] with regard to DCA hypertension, in this post-DCA "sustained" hypertension there does not appear to be any sodium and potassium disequilibrium. In other words, the evidence to date does not suggest that the hypertension is the result of a derangement in water balance.

We have tentatively suggested that a possible cause of this hypertension is an adrenal-renal imbalance. According to this hypothesis the kidney fails in its ability to excrete some normally occurring adrenal pressor material, DCA-like in nature. The experiments here reported add nothing to this suggestion except to indicate that, if a DCA-like material is implicated, it would have to lack the marked electrolyte effects of the synthetic steroid. Work in progress at present appears to indicate that Compound F might be such an agent, although for reasons as yet unexplained, this agent is more active in young than in older rats.

Recently, Green and associates[13] have confirmed our finding that "sustained" hypertension may follow a short period of intensive treatment with DCA. Like ourselves, these investigators have found no explanation for the persistent hypertension. They have, however, noted that the hypertension persists after adrenalectomy, a finding which would certainly negate our present hypothetical explanation.

SUMMARY

Rats subjected to a short period of intensive treatment with DCA may develop a sustained hypertension after cessation of treatment. The percentage of rats which remain hypertensive appears to depend on the severity of treatment.

Although a renal functional impairment is demonstrable in the post-DCA period, it occurs equally in those rats which do not sustain the hypertension and in those which do.

The renal handling of sodium and potassium in post-DCA animals differs slightly from that of control animals, but bears no observable relation to the presence or absence of hypertension.

Histologic study of both kidneys and adrenals fails to reveal any difference between normotensive and hypertensive animals.

The presence of a sustained hypertension, hitherto reported on the basis of indirect blood pressure observations, has been fully confirmed by direct electromanometry.

We are indebted to the Schering Corporation, Bloomfield, N. J., for the Cortate pellets used in these experiments.

REFERENCES

1. Selye, H., and Hall, C. E.: Pathologic Changes Induced in Various Species by Overdosage With Desoxycorticosterone, Arch. Path. **36:**19, 1943.
2. Perera, G. A., Knowlton, A. I., Lowell, A., and Loeb, R. F.: Effect of Desoxycorticosterone Acetate on Blood Pressure of Man, J. A. M. A. **125:**1030, 1944.
3. Eisenberg, S., Buie, R., Jr., and Tobian, L., Jr.: Adrenal Cortical Function in Essential Hypertension, A Study of Sweat Sodium Concentration, Am. J. M. Sc. **22:**287, 1950.
4. Friedman, S. M., Friedman, C. L., and Nakashima, M.: The Hypertensive Effect of Compound F Acetate in the Rat, Endocrinology, **51:**401, 1952.
5. Boland, E. W., and Headley, N. E.: Compound F Used Orally in Patients With Rheumatoid Arthritis, J. A. M. A. **148:**981, 1952.
6. Turner, L. B., and Grollman, A.: Role of Adrenal in Pathogenesis of Experimental Renal Hypertension as Determined by a Study of the Bilaterally Adrenalectomized Nephrectomized Dog, Am. J. Physiol. **167:**462, 1951.
7. Friedman, S. M., and Friedman, C. L.: Self-sustained Hypertension in the Albino Rat: A Hypothesis to Explain It, Canad. M. A. J. **61:**596, 1949.
8. Friedman, S. M., Friedman, C. L., and Nakashima, M.: Sustained Hypertension Following the Administration of Desoxycorticosterone Acetate, J. Exper. Med. **93:**361, 1951.
9. Friedman, S. M., Polley, J. R., and Friedman, C. L.: The Clearance of Inulin and Sodium p-Aminohippurate in the Rat, Am. J. Physiol. **150:**340, 1947.
10. Friedman, S. M., Friedman, C. L., and Nakashima, M.: Inhibition of Cardiovascular-renal Effects of DCA by Pitressin, Am. J. Physiol. **170:**270, 1952.
11. Zweifach, B. W., Black, M. M., and Shorr, E.: Histochemical Alterations Revealed by Tetrazolium Chloride in Hypertensive Kidneys in Relation to Renal VEM Mechanisms, Proc. Soc. Exper. Biol. & Med. **74:**848, 1950.
12. Braun-Mendenez, E.: "Hypertension, a Symposium" edited by E. T. Bell, Minneapolis, 1951, University of Minnesota Press, p. 161.
13. Green, D. M., Saunders, F. J., Wahlgren, N., and Craig, R. L.: Self-sustaining Post-DCA Hypertensive Cardiovascular Disease, Am. J. Physiol **170:**94, 1952.

FUNCTIONAL EVALUATION OF AN INTERNAL MAMMARY CORONARY ARTERY ANASTOMOSIS

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CORONARY artery disease in man is prevalent and ranks second only to other forms of cardiovascular disease and cancer as a cause of death. An analysis of the statistics on coronary artery disease and angina pectoris would seem to indicate that there has been a definite increase in the death rate from this cause in recent years. With medical treatment alone, approximately one out of two patients suffering from coronary artery disease have expired by the end of five years.[1,2,3] It is thus vitally important that some form of therapy be discovered both to prevent the progress of this disease and to relieve the patient of his or her distressing symptoms. In coronary artery disease there is either a slow or rapid diminution of arterial blood flow to the ventricular myocardium because of narrowing or blocking of the coronary arteries. The resultant myocardial ischemia causes death or progressive disability with or without anginal pain.

The treatment of coronary artery insufficiency has occupied the minds of clinicians and experimentalists for many years. At first, efforts to help patients suffering from angina pectoris were directed at relieving their pain. Many types of nerve sectioning operations were devised. The most frequently practised was that of dorsal sympathectomy.

Gradually, as a better understanding of the cause of anginal pain was acquired, it was observed that there was an association between anginal pain and myocardial ischemia. This concept of angina pectoris led to the development of surgical methods which were devised to increase the deficient coronary circulation. During the past seventeen years, led by Claude Beck and sparked by the development in thoracic surgery, many efforts have been made to increase the failing coronary circulation. The various surgical procedures which have been described may be grouped according to the manner in which arterial blood is brought to the ventricles.

I. SURFACE OF VENTRICLES

(a) *Grafts:* The first method attempted was to bring arterial blood to the surface of the ventricles. This has been accomplished by means of grafts, such as pectoral muscle, omentum, or lung. In these procedures, the graft is sutured to the surface of the left ventricle. It was hoped that new blood vessels would grow from the graft into the ventricular myocardium and thereby bring to it an additional arterial blood supply.

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Beck,[4] O'Shaughnessy,[5] and others have attempted this type of operation on human cases of coronary artery disease with questionable results.

(b) *Cardio-pericardiopexy:* Another method of bringing additional arterial blood to the ventricular myocardium is by the creation of granuloma between the parietal and visceral pericardium. This was first attempted by Beck, using powdered bone insufflated into the pericardial sac. He later used asbestos powder and other substances.

Thompson and other workers have placed different irritating substances into the pericardial sac. The most favorable of these is powdered talc. Thompson[6] has reported cardiopexy on fifty-two patients, the first being alive thirteen years after operation. He is of the opinion that this procedure has been helpful in rehabilitating a group of cardiac cripples. The procedure is simple and may be of value in helping incapacitated patients who are unable to undergo more extensive surgery.

II. CARDIAC VEIN LIGATION

By cardiac vein ligation, Fauteux[7] thought that interarterial anastomoses would be opened and that the ventricle would receive increased blood flow by means of the thebesian canals. After much animal experimentation, he performed this operation on some patients with coronary artery insufficiency. The results, however, are not well known because of Fauteux's untimely death.

III. ARTERIALIZATION OF THE CORONARY VENOUS SYSTEM

A completely new approach to the problem was devised by Beck and associates[8] when they anastomosed the aorta to the coronary sinus by means of a vein graft. By this method, extra coronary arterial blood is delivered to the myocardium along the coronary veins. This procedure has two stages, three to four weeks apart. At the first operation, the aorta is anastomosed to the coronary sinus through a free vein graft; at the second stage, the coronary sinus is partially occluded proximal to the site of the vein graft. In this way, arterial blood is forced into the coronary venous system. Arterialization of the venous system of the left ventricle has the advantage that, if successful, arterial blood should reach all parts of the ventricle. Its disadvantages are:

1. Technically the venous grafts are very difficult to place and require two separate operations, 10 days to 3 weeks apart.
2. A high percentage of the venous grafts are found to be thrombosed at the second stage.
3. An arteriovenous aneurysm is created.
4. Vein grafts tend to balloon after six months unless backed by fascia.

IV. ARTERIALIZATION OF THE INTRAMURAL VESSELS OF THE LEFT VENTRICULAR MUSCLE BY MEANS OF INTERNAL MAMMARY ARTERY IMPLANTATION

Before proceeding to the details of this method of revascularization of the ventricular muscle, a short review of the histologic, anatomic, and pathologic structure of the myocardium must be given. There are two factors now generally

accepted upon which the procedure of an internal mammary artery implant is based; one is the anatomic pattern of the myocardial circulation and the other is the modern concept of the pathology of coronary artery sclerosis.

1. *Anatomical Structure of the Ventricular Myocardium.*—It is well known that there are differences between cardiac and skeletal muscles. The differences in which we are most interested concern the peculiarly rich network of blood vessels which supply the myocardial muscle fibers. Actually, there exists within the myocardium a veritable sponge-work of vessels.[9] Their arrangement is graphically shown in Fig. 1. As the smaller branches of the coronary arteries subdivide, they leave the surface of the heart and penetrate the myocardium at right angles. As they approach the endocardial surface they resume their horizontal direction and arborize into a rich arteriolar bed from which the capillaries

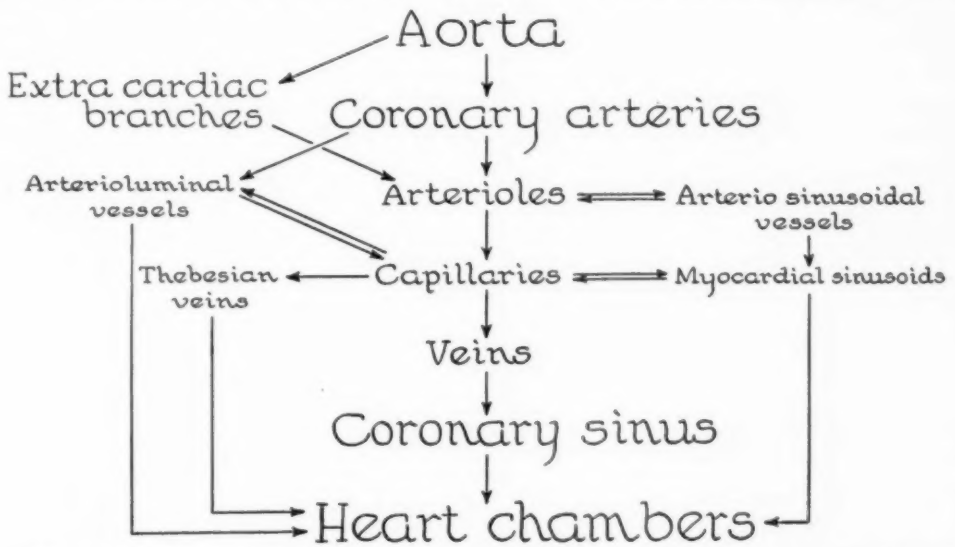


Fig. 1.—This figure graphically indicates the relationship between sinusoidio arterial vessels, myocardial sinusoids, arterioles, and capillaries.

arise. The arterioles also communicate directly with sinusoidal arterial vessels which connect with the myocardial sinusoids. These latter vessels with a lumen of from 50 to 250 mm. in diameter run a wandering course about the muscle fibers and anastomose with each other and the capillaries. Because of the structure of the myocardium, an implanted internal mammary artery with an open intercostal vessel fails to form a surrounding hematoma and remains patent for an indefinite period of time.

The second factor which indicates that internal mammary implant will be a successful method of treating coronary artery insufficiency is based on the pathological character and distribution of coronary artery disease.

2. *Pathology of Coronary Artery Disease.*—The generally accepted idea that coronary artery disease is widely spread thoughout the coronary tree has not been borne out by pathological study. Arteriosclerosis of the coronary arteries is usually, if not always, confined to the epicardial part of their courses and never

involves the penetrating myocardial branches to any significant degree.[10,11] Thus, in coronary artery sclerosis there is a vast network of arterioles, and so forth, deep within the myocardium, which are free of disease. If arterial blood is delivered to this network, then it can reach all parts of the ventricular myocardium. An implanted internal mammary artery thus can bridge over the blocked superficial coronary vessels so that arterial blood can reach the intact deep arteriolar system of vessels which are still open and free of disease. With these facts in mind a different approach to the vascularization of the myocardium was first attempted by us in 1945.

INTERNAL MAMMARY ARTERY IMPLANT

Procedure.—The left internal mammary artery is freed from the chest wall from the fourth to the sixth intercostal space. The distal end is doubly ligated and transected between the ligatures. A tunnel is made in the anterior wall of the left ventricle and the freed portion of the artery is pulled into the tunnel and there fixed. The intercostal vessels which arise from the freed portion of the internal mammary artery are ligated except for the sixth which is transected just before the implant is pulled into the myocardial tunnel. The internal mammary artery is thus placed in a tunnel within the ventricular myocardium, with an open freely bleeding intercostal branch (Fig. 2).

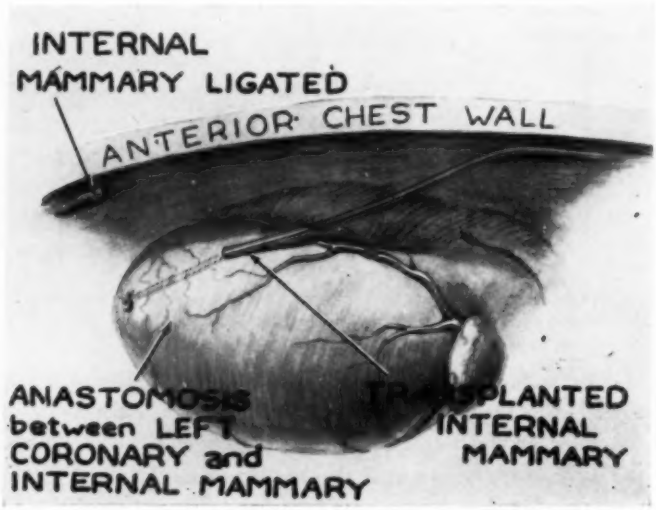


Fig. 2.—Drawing showing internal mammary artery implant.

Results.—In previous publications,[12-18] it was shown that an anastomosis developed between the implanted internal mammary artery and the left coronary circulation. The proof of the presence of this anastomosis was established by injection studies, radiographs, serial sections, and plastic casts (see Figs. 3-9).

Weeks or months after implantation, the animals were sacrificed. Separate cannulas were inserted into the internal mammary and the left coronary artery. The heart and attached internal mammary artery were removed from the thoracic cavity and Schlesinger's injection mass was introduced through the internal

mammary artery. It passed freely through no vessel smaller than an arteriole 40 microns in diameter. When there was a large anastomosis, the injection mass was seen to enter the internal mammary artery, spread throughout the coronary arteries of the left ventricle, and fill the cannula placed in the left coronary artery (Fig. 7). This would indicate that the anastomosis is with the arterial rather than the venous side of the coronary circulation.

Fig. 3.

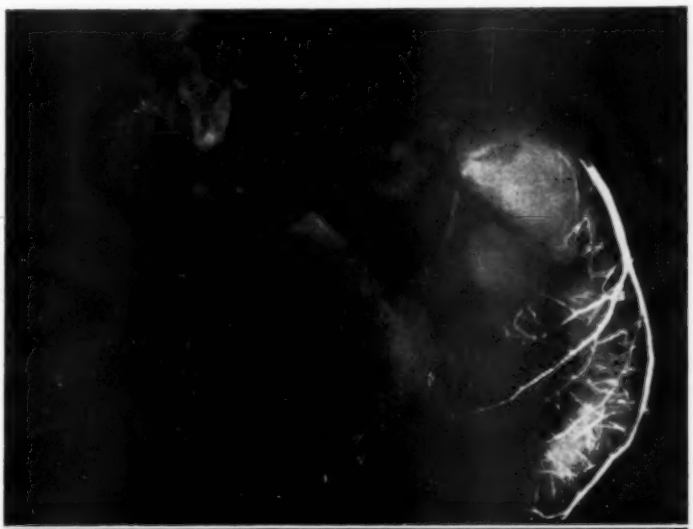


Fig. 4.

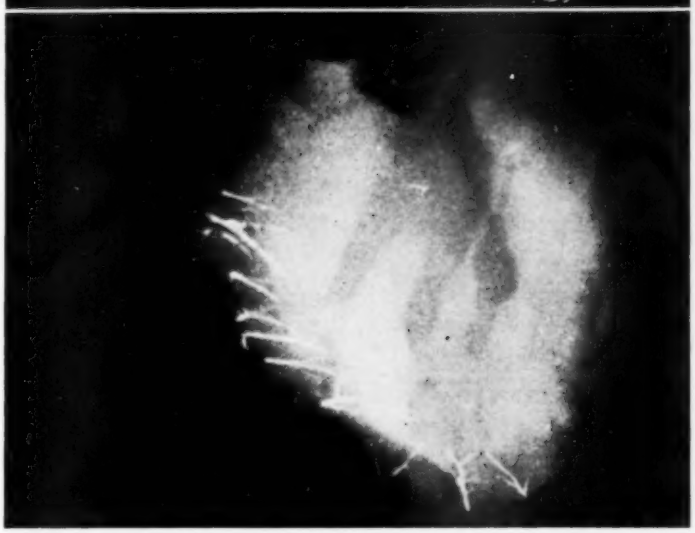


Fig. 3.—Photo of radiograph of unrolled heart of dog No. 9, Series A, Group 1, showing extent of the filling of the left coronary artery by injecting the internal mammary artery with Schlesinger's solution three months after implantation into the left ventricular wall.

Fig. 4.—Photo of radiograph of the excised interventricular septum from dog No. 9, Series A, Group 1. This photo illustrates how the septal branches are filled by injecting theinternal mammary artery after implantation.

Duration of Coronary Mammary Anastomosis.—Glenn and associates[19] have confirmed the development of an anastomosis between an implanted internal mammary artery and the coronary vessels. However, they stated that the new vessels tend to disappear at the end of eight weeks. They further suggested that the new vessels were small and resembled granulation tissue.

In our series, the average interval from implant to sacrifice was eleven weeks (Table I). One animal was kept fifty-eight weeks after implantation. The anastomoses at the end of that time not only persisted but were large enough to protect against death and infarction following ligation of the anterior descending branch of the left coronary artery.

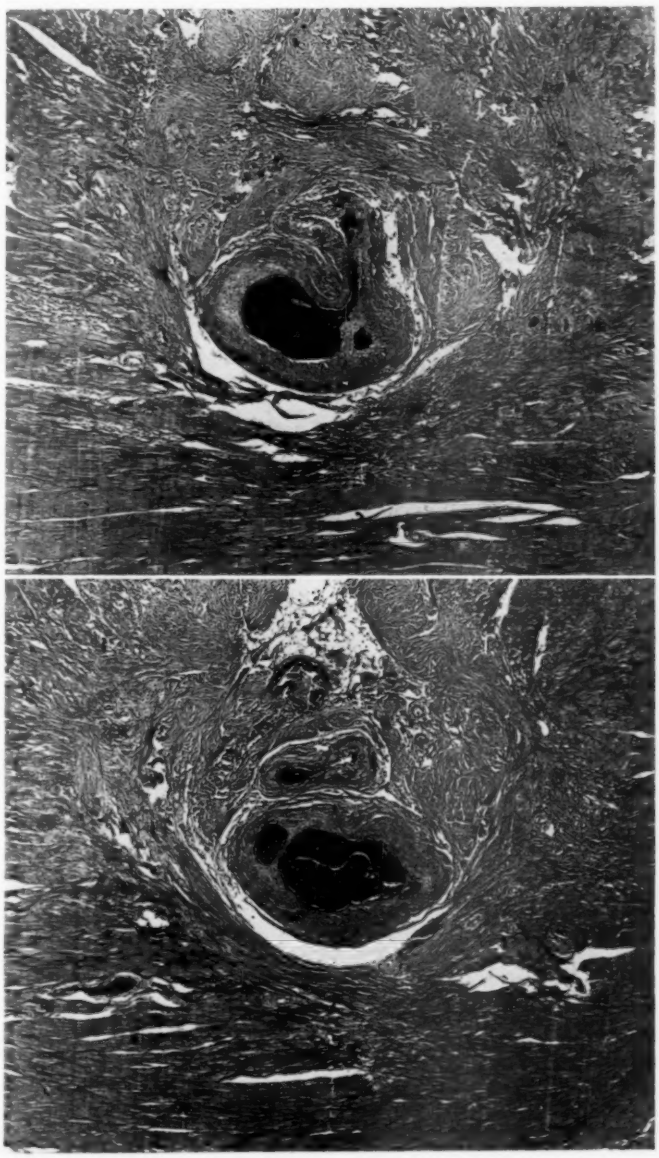
TABLE I. DURATION OF ANASTOMOSIS

TYPE OF ANASTOMOSIS	NO. OF ANIMALS	PRESENCE OF ANASTOMOSIS AFTER IMPLANT (WEEKS)	VALUE OF ANASTOMOSIS AFTER LIGATION OF ANTERIOR DESCENDING BRANCH, LEFT CORONARY ARTERY
Microscopic anastomosis	1	5	
	1	6	
	1	7	
Anastomosis small	2	8	Protection against death or infarction afforded in 3 animals only
Due to thickened or partially thrombosed internal mammary artery	2	11	
	2	12	
	2	13	
	1	14	
	12		
Macroscopic anastomosis	1	6	
	2	7	
	5	9	
	5	11	No deaths or infarction occurred
Anastomosis large	4	12	
	2	14	In Cellophane coronary artery sclerosis caused by Cellophane wrap
Internal mammary artery patent	1	17	
	1	18	
	3	19	
	1	21	
	1	31	
	1	41	
	1	46	
	1	58	
	29		

Character of Coronary Mammary Anastomosis.—Not only has it been suggested that a coronary mammary anastomosis tends to disappear at the end of eight weeks, but it has also been suggested that the anastomosis is capillary in character. Serial section studies of seven implants have been examined. Special stains of these serial sections have been made to show elastic and muscle tissue. The character of the new branches formed by the internal mammary artery implant have thus been studied. They have been found to be arterial in nature, containing both muscle and elastic tissue in their walls. These new arterial branches have been followed by serial section far out into the myocardium until they disappear.[20]

Factors Influencing the Formation of Internal Mammary Coronary Artery Anastomosis.—It was soon established that in certain cases large anastomotic channels quickly developed between the implanted internal mammary artery and the coronary circulation. In the earlier experiments there was a 60 per cent failure

A.



B.

Fig. 5.—Microphotograph of serial sections of dog No. 181, survived anterior descending branch of left coronary artery ligation sixteen weeks after internal mammary artery implantation. The internal mammary artery has been injected with blue Schlesinger's dye. Note branching of transplant with injection mass in lumen and in the vessels surrounding myocardium. *A.* Microphotograph Serial section No. 3. *B.* Microphotograph Serial section No. 4 (elastic stain).

rate, but further experimentation established the following circumstances as most valuable in securing a widely patent anastomosis:

(a) as short a length as possible of the internal mammary artery should be freed from the chest wall;

(b) the implanted portion of the artery should be placed in the inner two-thirds of the myocardium;

(c) an intercostal branch of the implanted portion of the internal mammary artery should be left patent.

It is also important to avoid extensive trauma of the implant and infection of the pericardial and pleural cavities. The presence of infection favors the formation of a thrombus in the implanted artery. Although anastomoses have developed by recanalization of a thrombosed vessel, their caliber is seriously limited. By observing these factors, an anastomosis can be produced in from 50 to 75 per cent of the experiments.

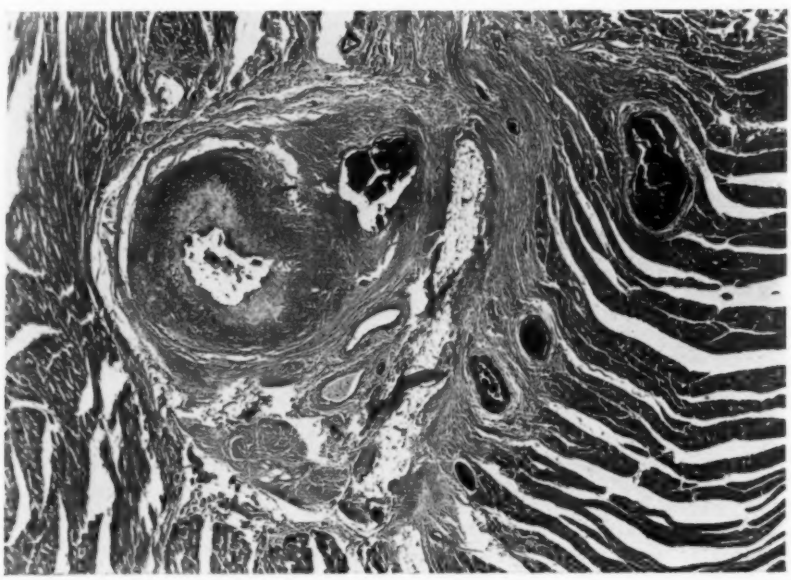


Fig. 6.—Microphotograph of dog No. 170, survived anterior descending branch ligation of the left coronary artery nineteen weeks after internal mammary artery implantation. The implanted internal mammary artery has been injected with blue Schlesinger's solution. Section shows arteries of relatively large size in myocardium surrounding transplant, vessels filled with injection mass; they represent either tremendous expansion of pre-existing vessels or new vessels, most likely the latter.

In more recent experiments there is evidence that the presence of coronary artery insufficiency tends to favor the formation of an anastomosis. The favorable influence of coronary artery insufficiency is demonstrated both in the total number of anastomoses produced, as well as in the size and quality of the anastomotic channels.

Value of Coronary Mammary Anastomosis.—Histoanatomic proof of anastomotic channels between extracardiac arterial sources and the coronary circulation gives no indication of its functional value. This is not only true of coronary

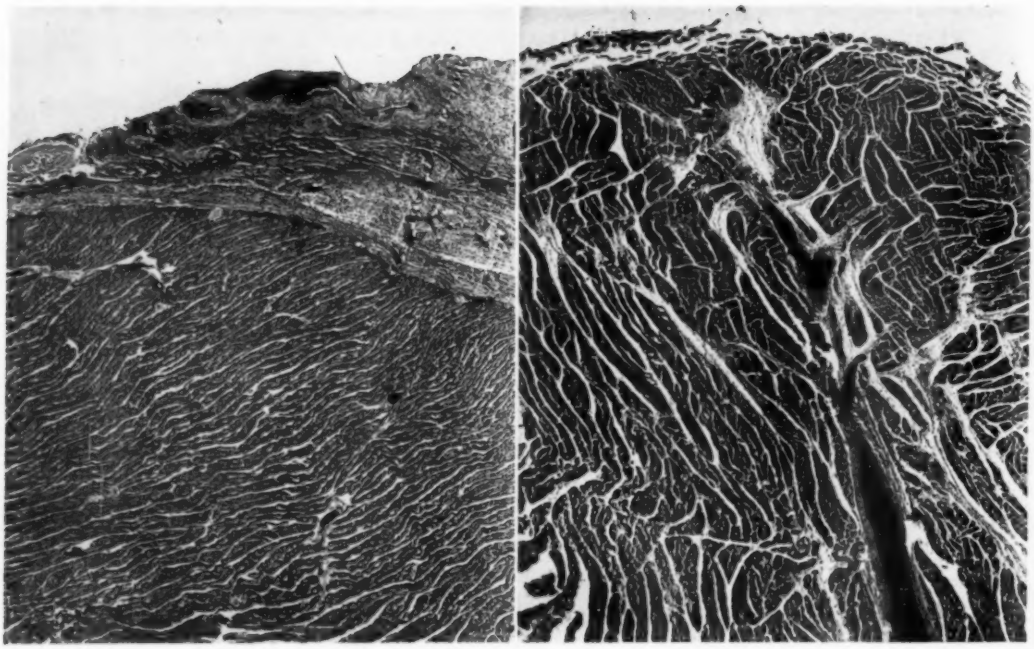
mammary artery anastomosis but of all other procedures used for augmenting myocardial circulation.

Functional tests give the best indication of the value of the new arterial blood supply. These may be divided into three groups.

I. *Survival Experiments Following Ligation of the Anterior Descending Branch of the Left Coronary Artery.*—There is some divergence of opinion in the literature as to the effects of ligation of the anterior descending branch of the left coronary artery. There are those who claim a low mortality for this procedure, and others who claim a high mortality. The majority of investigators have found the mortality in dogs ranges from 70 to 80 per cent. In our series of ten control dogs, the average mortality rate from anterior descending branch ligation was 80 per cent. It is our belief that the great variation in mortality reported in the literature following anterior descending branch ligation is dependent upon the site of the ligation.

Fig. 7.—Photos of injected internal mammary artery of dog No. 185, Series 2, seven weeks after implantation; this animal survived anterior descending and circumflex artery ligation. *Note:* The glass cannula in the left coronary artery (top right) is filled with the injection solution which was introduced through the implanted internal mammary artery (lower left). This would indicate that the anastomosis is with the arterial rather than the venous side of the coronary circulation.

The anterior descending branch of the left coronary artery should be ligated at its origin. The position of the ligature must be carefully checked by examining the left coronary artery to make certain that the ligature has included all branches other than the circumflex. Frequently one or two septal branches are missed and occasionally branches arise directly from the main trunk of the left coronary artery.



A. *B.*

Fig. 8.—Sections of myocardium and left ventricle of dog No. 185 described in Fig. 7. Separate sections have been taken through the epicardium and endocardium, respectively. Note how the injection mass (after injection into the implanted internal mammary artery) has spread throughout the vessels of the myocardium. *A* shows the vessels of the epicardium filled with the dye and *B* the vessels of the endocardium.

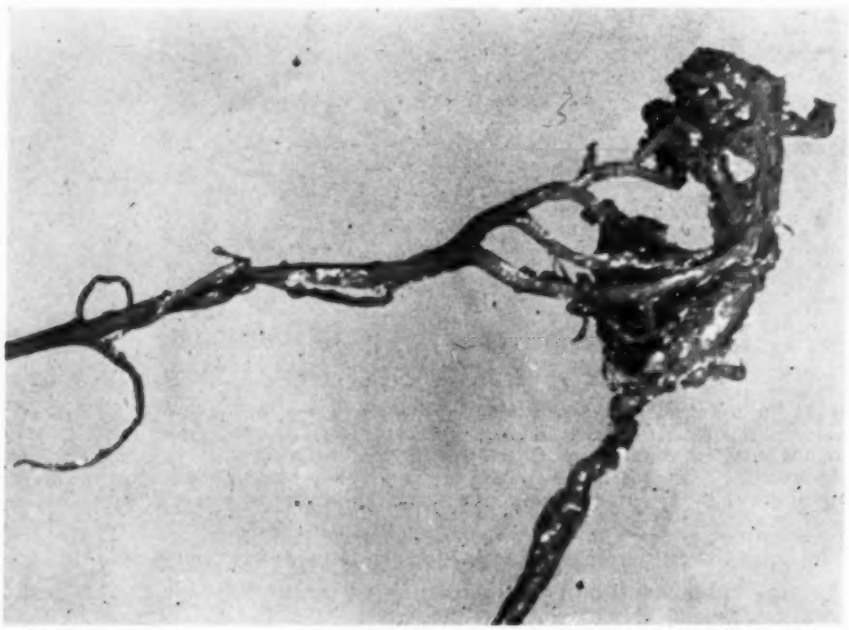


Fig. 9.—The manner of mammary-coronary artery anastomosis is probably best shown in a cast made by injecting the internal mammary artery 22 weeks after implantation with an acid resistant rubber compound. Note the new branches of the implanted mammary artery (bottom) which join with those of the anterior descending branch of the left coronary artery (left). A piece of polyethylene tubing was tied around the anterior descending branch at its origin before digestion was started.

An analysis of the results of anterior descending branch ligation is shown in Table II. A total of 78 dogs had anterior descending branch ligation. There were ten control animals and thirty-nine other animals in whom the coronary circulation was not augmented. In this group of animals there was an over-all 80 per cent mortality with a 20 per cent survival with infarction. In twenty-nine animals in whom a large mammary coronary anastomosis had developed there were no deaths and no infarctions following anterior descending branch ligation. Thus it would seem that coronary mammary anastomosis not only increases coronary circulation but gives protection against death and infarction.

The experimental data shown in Table II indicates that coronary mammary anastomosis when it occurs is of value in protecting against death or infarction.

TABLE II. EXPERIMENTAL DATA*

	LIGATION ANTERIOR DESCENDING BRANCH OF THE LEFT CORONARY ARTERY			
	NO. OF DOGS	DEATH	SURVIVAL WITH INFARCTION	SURVIVAL WITHOUT INFARCTION
Control	10	80%	20%	0
Internal Mammary Artery Implant and/or other experiments but without augmentation of the coronary circulation	39	80%	3%	17%
Internal Mammary Artery Implant with coronary anastomosis	29	—	—	100%

Note: Internal mammary artery after implantation forms anastomoses with coronary circulation in from 50 to 75 per cent of animals operated upon.

*Vineberg and associates

The experimental data shown in Table II indicates that coronary mammary anastomosis when it occurs is of value in protecting against death or infarction. However, because of the difference of opinion concerning the value of survival after anterior descending branch ligation, a second group of functional experiments were performed.

II. *Direction of Blood Flow in Implanted Internal Mammary Artery.*—The direction of blood flow through the implanted internal mammary artery was studied in order to determine whether it was bringing blood to the ventricular myocardium. Direct determination of the direction of blood flow in the internal mammary artery was difficult, so the indirect method was used. Animals which survived anterior descending branch ligation of the left coronary artery were subjected four to five weeks later to complete and sudden occlusion of the implanted internal mammary artery. If the internal mammary artery was maintaining the circulation of the left ventricle, then following its ligation either death or infarction should result. In three animals with an internal mammary implant which had survived anterior descending branch ligation, the internal mammary artery was ligated. One animal died within 24 hours and displayed an edematous cyanotic area of the anterior wall of the left ventricle. One survived for three

days before dying from a large infarct in the same location (Fig. 10). The third animal survived, but examination of the sacrificed specimens revealed that multiple intercoronary anastomoses were present.

In all of these animals there was a demonstrable mammary coronary artery anastomosis.

In those animals that died following internal mammary artery ligation there can be little doubt that the circulation of the anterior portion of the left ventricle was being maintained by the internal mammary artery implant.

The evidence just presented suggests that the internal mammary artery after implantation into the left ventricular wall is capable of maintaining the left ventricular circulation. These experiments, however, were carried out on the hearts of normal animals. It was, therefore, necessary to attempt artificially to produce coronary artery insufficiency and to treat it by internal mammary artery implantation.

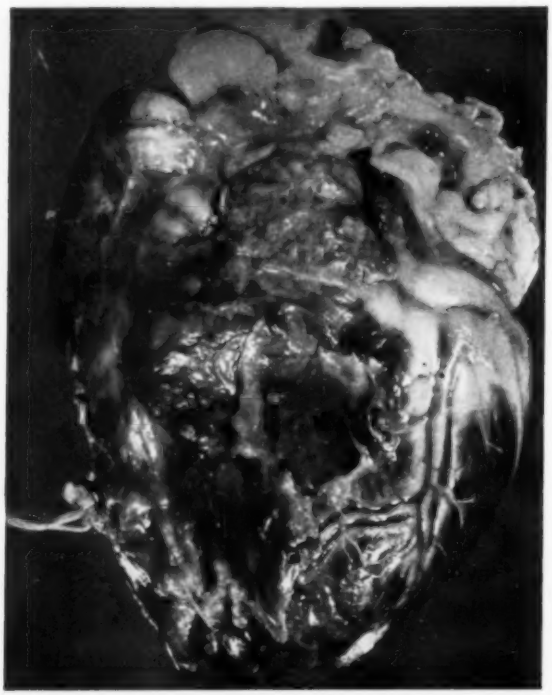


Fig. 10.—Photo of heart of dog No. 10, Series A, Group B. This animal withstood anterior descending branch ligation 67 days after internal mammary artery implant. Thirty-six days later the thorax was reopened and the implanted mammary artery was ligated. This resulted in ectopic beats and cardiac irritability. The animal died 3 days postoperatively. A large 3 x 3 cm. left ventricular anterior wall infarct was found. Perfusion of the internal mammary artery showed free communication between the implant and the left coronary tree, but not the right.

Thus we set out to produce experimentally and to treat coronary artery insufficiency, and so establish a third functional test of the value of an internal mammary coronary anastomosis.

III. *Experimental Production and Treatment of Coronary Artery Insufficiency.*—In this series of experiments coronary artery insufficiency was produced in dogs and treated by internal mammary artery implant. The first problem was

to find a method of producing coronary artery occlusion which would simulate that which occurred in human coronary sclerosis.

The second problem concerned the evaluation of coronary insufficiency when it was produced and its response to treatment.

Method of Producing Coronary Artery Insufficiency.—The anterior descending branch of the left coronary artery was exposed at its origin. Beneath the left auricular ventricular sulcus to the left of the pulmonary trunk the epicardium overlying the vessel was incised and the bifurcation of the main left coronary artery was exposed. A doubly folded strip of Cellophane (DuPont P.T. 300) sterilized for 24 hours in a saturated solution of mercury oxycyanide was twice wrapped completely but loosely around the origin of the anterior descending branch of the left coronary artery and fixed in position. Thus a segment of artery from 4 to 8 mm. long was completely surrounded with Cellophane.

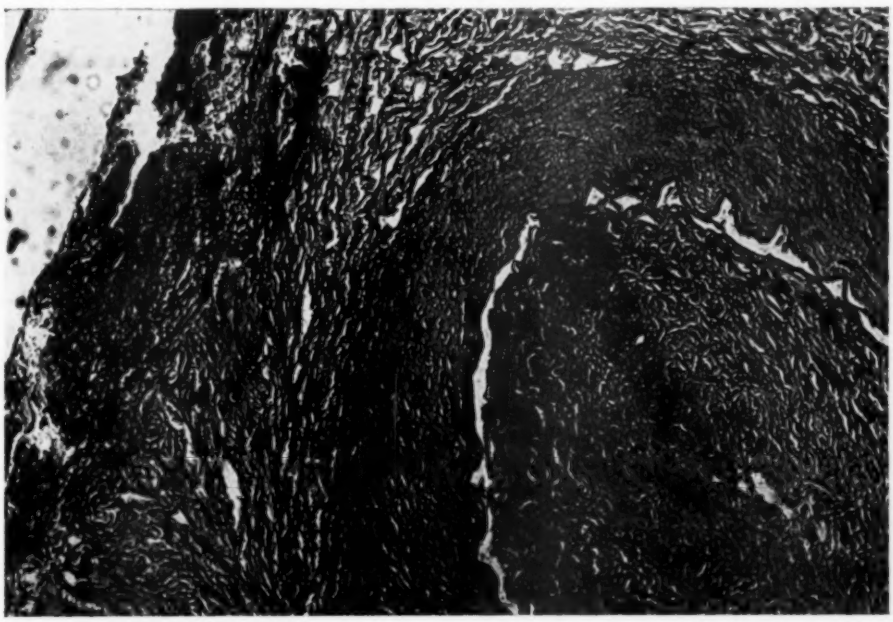


Fig. 11.—Section through anterior descending branch of the left coronary artery of dog No. 185, showing degree of occlusion of arterial lumen produced by sclerosing type Cellophane (DuPont PT—300).

The Cellophane initiated a fibroplastic reaction with collagen deposition about the artery. As subsequent contracture of the new fibrous tissue occurred, the lumen of the anterior descending branch of the left coronary artery was slowly narrowed. Gradually that portion of the myocardium nourished by this vessel became ischemic.

At the end of the experiment, when the animals were sacrificed, the anterior descending branch of the left coronary artery was probed to determine the extent of narrowing. Sections were made through the artery at the site of the Cellophane wrap and careful histological studies made of the degree of coronary occlusion (Fig. 11).

Method of Evaluation of Experimentally Produced Coronary Insufficiency and its Treatment.—

Exercise Tolerance Test: In human coronary artery insufficiency there are two outstanding symptoms, namely substernal pain and intolerance to exercise. In the dog it is most difficult to detect the presence of pain, but not difficult to determine accurately the animal's tolerance or intolerance to exercise.

Clinical experience has associated progressive exercise intolerance with myocardial ischemia. Thus, in the experimental animal, diminution of exercise tolerance has been accepted as evidence of myocardial ischemia. In this series of experiments, myocardial ischemia was produced by a Cellophane wrap placed around the origin of the anterior descending branch of the left coronary artery (see above). Exercise tolerance studies were carried out before and after the Cellophane wrap. Later, after an internal mammary artery implant, these studies were repeated in order to establish if any improvement had occurred.

A treadmill was used to exercise the animals. This was made originally for man and was thus very satisfactory for exercising large animals. The treadmill consisted of an endless leather belt mounted between two electrically driven steel drums. The available exercising platform was approximately 8 ft. by 2 ft. The movement of the belt could be controlled, and a clocking device continuously registered the speed in miles per hour. In this way a controlled quantity of exercise could be administered for any required time. The dogs were led onto the movable platform and encouraged while the mechanism was set slowly in motion. The speed was gradually increased until the dogs were running at a rate comparable to eight and one-half miles per hour. The exercise was continued until the animals became exhausted or ceased to run because of distress. The average running time for the animals before operation, or presumably before the development of myocardial ischemia, was 9 to 12 minutes at eight and one-half miles per hour. At this time the animals became tired and began to lag on the mill and would break alternately from a gallop to a run. Eventually the animals became anxious to escape the mill and exercise was discontinued. Such animals would avidly drink water. In three to four months after the Cellophane was placed about the anterior descending branch of the left coronary artery the dogs would tolerate only 2 to 4 minutes of exercise before becoming extremely anxious, whining and salivating profusely. If the mill was not stopped they would attempt to lie down or drag their feet on the revolving belt. When the exercise was stopped they would drop where they stood and for some minutes would resist all coaxing to move. They showed no interest in drinking water. When these latter symptoms developed, electrocardiographic changes indicative of myocardial ischemia were apparent. It was thus postulated that the decrease in exercise tolerance was due to the development of myocardial ischemia and that the acute symptoms displayed by these animals were the canine counterpart of human angina pectoris.

Twenty-five dogs were trained on the treadmill, their running time recorded, and they were subsequently operated upon. Cellophane (DuPont P.T.—300) was wrapped around the first 1.5 cm. of the anterior descending branch of the left coronary artery. Ten of these animals survived the procedure, the remainder died of ventricular fibrillation at the time of operation or postoperatively from

pneumonia, empyema, or distemper. After these animals had satisfactorily recovered from this operation their exercise tolerance was periodically determined.

Of the ten surviving animals, four were kept for control studies and the remaining six had an internal mammary artery implant after their exercise tolerance had been reduced from 9 to 12 minutes to 2.5 to 4 minutes. This occurred approximately three months after the Cellophane wrap. Only three animals of the six survived the internal mammary implant procedure. One animal died of distemper, two died of empyema.

After recovery the three surviving animals were again exercised periodically and three to five months after the implant operation the exercise tolerance of two of these animals was 6 to 8 minutes, respectively, whereas the four control animals had an average exercise tolerance of 1.6 minutes. All three of the mammary artery implanted animals showed evidence of a large internal mammary coronary anastomosis. The one animal whose exercise tolerance did not improve after implant was found to have a large substernal abscess. This presumably accounted for its failure to increase its tolerance after implant. Careful studies and sections were made of the site of the Cellophane wrap and injection studies were carried out by the previously described techniques.

Another group of experiments was carried out in which the Cellophane wrapping procedure was performed simultaneously with the internal mammary artery implant. In this group there were six animals, one of which died postoperatively from pneumonia. The five surviving animals were studied for four months. Two of the animals had a reduction in exercise tolerance to 2 to 3 minutes, respectively. When sacrificed these animals showed no significant internal mammary coronary artery anastomosis. The exercise tolerance of the remaining 3 animals was maintained at slightly below preoperative levels.

When these animals were sacrificed, two were found to have widely patent internal mammary coronary anastomosis. The remaining animal was found to have developed an anastomosis with the coronary venous circulation. This was the first instance in which this had occurred in our experience. The anterior descending branch of the left coronary artery in all of these animals showed marked narrowing at the site of the Cellophane wrap (Fig. 11).

CONCLUSIONS

Like many others, we are of the opinion that coronary artery disease is limited to the epicardial vessels. The vessels within the myocardium are, for the most part, not diseased. There exists, therefore, within the myocardium, a vast network of patent vessels capable of carrying arterial blood to the myocardium. We are of the opinion that fresh arterial blood reaches this network when an internal mammary artery is placed with an open sixth intercostal artery between the myocardial fibers. We believe that the estimation of the value of experiments designed to revascularize the myocardium should be based on functional studies. In our experiments, which include three main groups of functional studies, we have shown that the internal mammary artery after implantation into the myo-

cardium is capable of maintaining the circulation of the left ventricle after complete or partial occlusion of the anterior descending branch of the left coronary artery.

Because of the foregoing experimental studies, it was thought that internal mammary artery implantation might be of value in the treatment of human coronary artery insufficiency.

ADDENDUM

To date nine human patients with coronary artery insufficiency have undergone internal mammary artery implantation. The results have been most encouraging and will be published in a future article.

REFERENCES

1. Dominion Bureau of Statistics, Vital Statistics for Canada, Ottawa, 1949.
2. Statistical Bureau, Metropolitan Life Insurance Company Folder 29, #12, December 1948.
3. Parker, R. L., Dry, J. J., Willius, F. A., and Gage, R. P.: J. A. M. A. **131**:95, 1946.
4. Beck, C. S., and Tichy, V. L.: Am. Heart J. **10**:849, 1935.
5. O'Shaughnessy, L.: Lancet **1**:185, 1937.
6. Thompson, S. A.: Discussion Paper, J. Thoracic Surg. **23**:42, 1952.
7. Fauteux, M.: Surg. Gynec. & Obst. **71**:151, 1940.
8. Beck, C. S., Stanton, E., Batinchok, W., and Leiter, E.: J. A. M. A. **137**:436, 1948.
9. Wearn, J. T., Mettier, S. R., Klumpp, T. G., and Zachiesche, L.: Am. Heart J. **9**:143, 1933.
10. Schlesinger, M. J.: Am. Heart J. **15**:528, 1938.
11. Schlesinger, M. J.: Arch. Path. **30**:403, 1940.
12. Vineberg, A. M.: Canad. M. A. J. **55**:117, 1946.
13. Vineberg, A. M., and Jewett, B. L.: Canad. M. A. J. **56**:609, 1947.
14. Vineberg, A. M., and Niloff, P. H.: Gynéc. et obst. **91**:551, 1950.
15. Vineberg, A. M., Niloff, P. H., and Miller, D.: Proc. Royal Coll. Physicians and Surgeons, Dec. 1950.
16. Miller, D., and Vineberg, A. M.: Proc. Surg. Forum & Amer. Coll. of Surg., 294-299, Boston, Oct. 1950.
17. Vineberg, A. M., and Miller, D.: Canad. M. A. J. **64**:204, 1951.
18. Vineberg, A. M.: Jour. Thoracic Surg. **23**:42, 1952.
19. Glenn, F., Hulswade, G., and Gore, Arthur L.: Surgical Forum Clinical Congress of the American College of Surgeons, 289-293, 1950.
20. Vineberg, A. M., and Bencosme, S. A. (In Press.)

VALVULAR STENOSIS AS A CAUSE OF DEATH IN SURGICALLY TREATED COARCTATION OF THE AORTA

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PRIOR to the development of surgery adequate for the successful treatment of coarctation of the aorta, the demonstration of associated valvular disease was largely academic. Now that surgery offers the patient with coarctation of the aorta an excellent chance for a complete and permanent cure, the detection of the valvular lesions, both congenital and acquired, which are associated at times with coarctation of the aorta has become most important. Three cases are presented emphasizing the poor prognosis of patients operated upon for coarctation of the aorta who have coexisting aortic, subaortic, or mitral stenosis.

CASE REPORTS

Case 1.—R. S., a 2-year-old boy, was admitted to the Los Angeles County Hospital on September 27, 1950, with a history of having had a known cardiac murmur since the age of 8 months. The child's growth was poor, and it was noted particularly that the chest and upper extremities were developed to a much better degree than the lower extremities. The child had never walked and was short of breath while crawling. Cyanosis was absent.

The blood pressure was 120/80 mm. Hg in the right arm, 150/80 mm. Hg in the left arm, and 0/0 in both legs. The apex impulse of the heart was in the axillary line. A systolic thrill and Grade 3 systolic murmur were present in the left third and fourth intercostal spaces just medial to the cardiac apex. A Grade 4 systolic murmur, transmitted to the neck vessels but not accompanied by a thrill, was heard in the aortic area. The aortic second sound was normal. One observer heard a diastolic apical murmur.

The electrocardiogram showed a vertical heart with clockwise rotation and some evidence of right ventricular hypertrophy.

Roentgenogram examination of the chest showed moderate generalized cardiac enlargement and pulmonary congestion. The cardiac pulsations were vigorous and regular. There was no notching of the ribs (Fig. 1, *A* and *B*).

Angiocardiography was done on September 29, 1950. The right ventricle was dilated but the pulmonary artery appeared normal. The left auricle was enlarged and was more densely opacified and retained the contrast medium for a longer time than we were accustomed to see (Fig. 1 *C*). These findings were noted at the time of examination but their significance was not appreciated. The left ventricle was seen only in systole, and its size could not be determined accurately. The ascending aorta was slightly dilated. The site of coarctation was not visualized.

The preoperative diagnosis was coarctation of the aorta and interventricular septal defect.

Operation was performed on November 2, 1950. A coarctation with marked narrowing of the lumen of the aorta was present 1.5 cm. below the origin of the left subclavian artery at the

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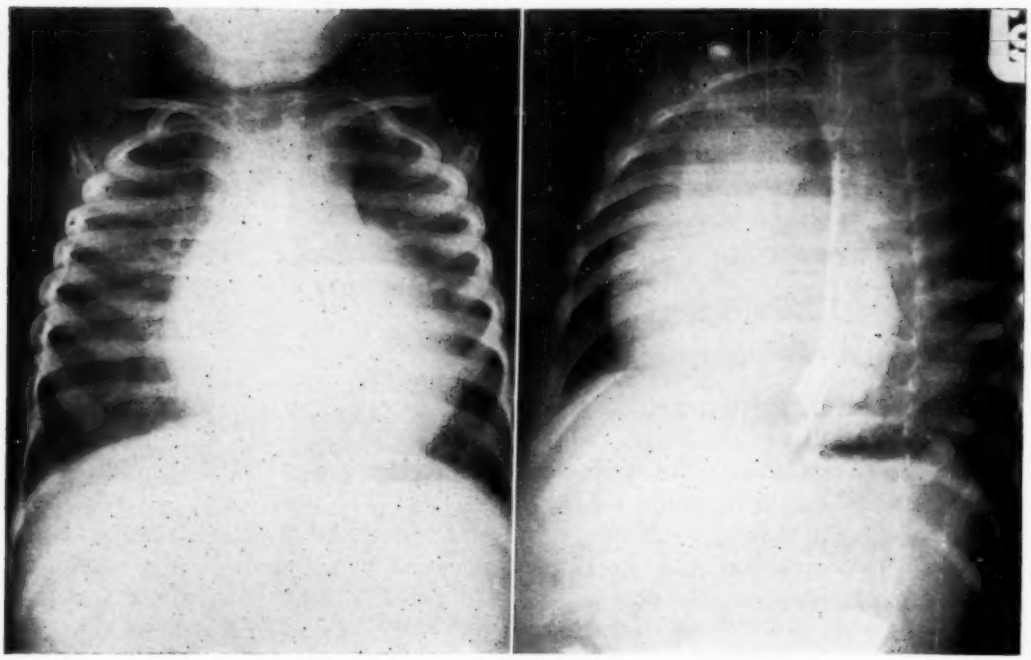


A. *B.*

Fig. 1 A and B (Case 1).—Coarctation of the Aorta and congenital mitral stenosis. *A*, Posteroanterior and *B* left oblique views. Congestive heart failure. Generalized cardiac enlargement without demonstrable specific enlargement of the left auricle.

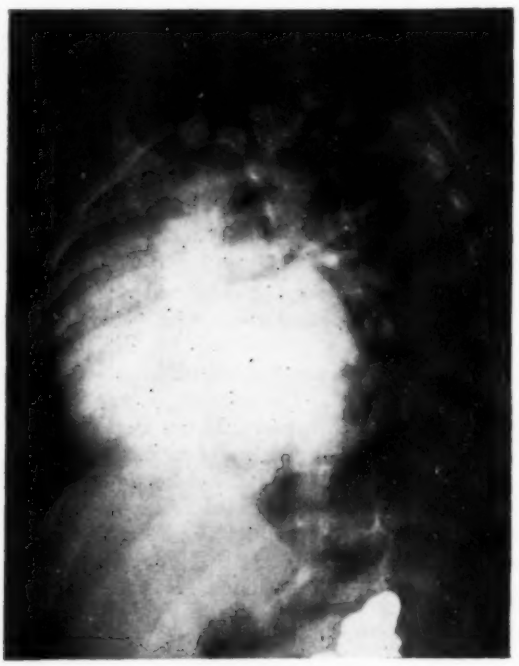


Fig. 1*C*.—Angiocardiography. Enlargement of the left auricle with increased and prolonged opacification. Though the ascending aorta is visualized, the coarctation itself is not demonstrated.

point of the insertion of a nonpatent ligamentum arteriosum. After the latter had been incised and the aorta freed, preparatory to excising the coarctation, bradycardia developed. Despite all attempts at cardiac resuscitation, the heart stopped beating in diastole and could not be revived.

Autopsy.—The heart weighed 175 grams. The right auricle and ventricle and left auricle were moderately dilated. The myocardium of the left ventricle measured up to 12 mm. in thickness, the right ventricle up to 7 mm., and the left auricle up to 3 mm. The endocardium of both ventricles was opaque and thickened. The mitral valve was markedly stenotic with only a 5 mm. opening at the depth of the fibrous, fused valve cusps. The other valves were normal. There was no interventricular septal defect. A coarctation of the aorta with only a pin-point lumen was present just distal to the origin of the left subclavian artery.

Case 2.—G. B., a 7-year-old boy with a known cardiac murmur since the age of 18 months was admitted to the Los Angeles County Hospital, January 25, 1950. The presenting complaints were weakness and shortness of breath, slowly increasing over a period of five years and culminating shortly before admission to the hospital in mild cardiac failure. He had had repeated upper respiratory infections and one episode of pneumonia. Cyanosis had been noted during exertion and the child would squat when fatigued.

The patient was poorly nourished, underdeveloped, cyanotic, and dyspneic. The cyanosis disappeared and the dyspnea improved markedly with oxygen therapy. The blood pressure was 80/60 mm. Hg in the right arm, 100/75 mm. Hg in the left arm, and 0/0 in both legs. The apex impulse of the heart was in the anterior axillary line. The cardiac rate and rhythm were normal. The aortic and pulmonic second sounds were equal and normal in intensity. A harsh systolic murmur and thrill were present at both the aortic and pulmonic areas and were widely transmitted over the chest, back, and neck vessels. On one occasion a harsh Grade 2 to 3 aortic diastolic murmur was heard. The breath sounds were diminished at the right base, but the lungs were clear otherwise. The liver was enlarged. There was no peripheral edema. Six toes were present bilaterally, and a sixth finger had been amputated from each hand.

The electrocardiogram showed the pattern of left ventricular hypertrophy.

On admission, there was radiographic evidence of congestive failure. There was moderate cardiac enlargement predominantly in the region of the left ventricle. Notching of the ribs was not evident (Fig. 2, *A*).

The patient improved rapidly and was discharged from the hospital. On April 25, 1950 he was readmitted to the hospital suspected of having subacute bacterial endocarditis because of anemia, splenomegaly, and fever. Improvement followed three weeks of chemotherapy.

Angiocardiography was performed on May 26, 1950. There was evidence of an increase in the circulation time as indicated by only faint opacification of the left auricle and failure to visualize either the left ventricle or aorta nineteen seconds after the dye had been injected.

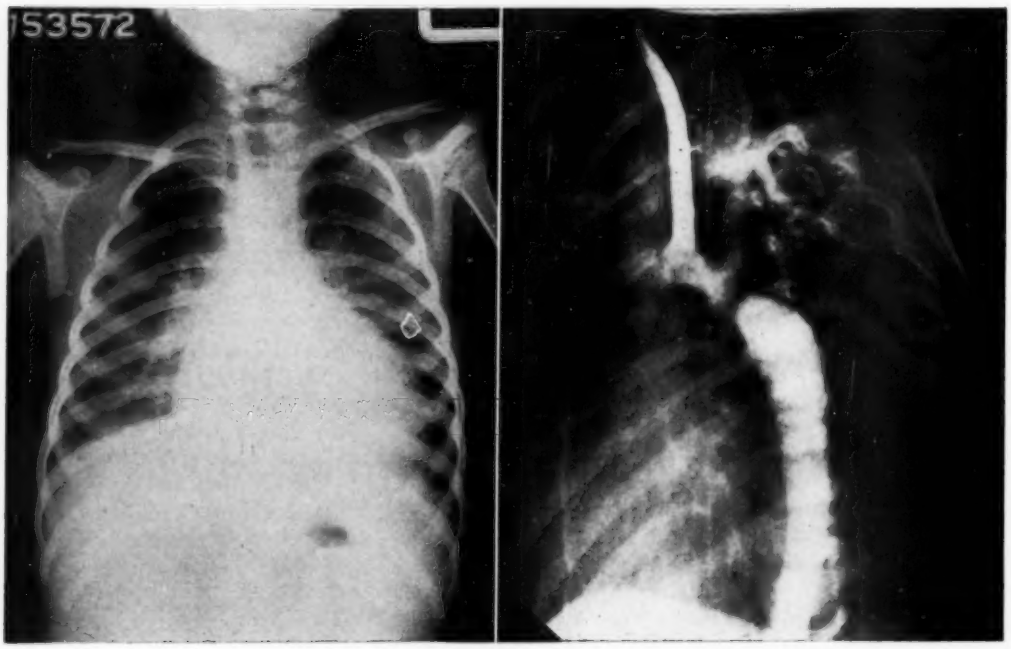
Retrograde aortography utilizing the left carotid artery was performed on September 1, 1950. A narrow band-like constriction was seen immediately beyond the origin of the left subclavin artery. There was a moderate degree of poststenotic dilatation extending a considerable distance beyond the coarctation. Numerous dilated collateral vessels were visualized (Fig. 2, *B*).

The preoperative diagnosis was coarctation of the aorta with probably a coexisting bicuspid aortic valve or either aortic or subaortic stenosis.

An operation was performed September 11, 1950. The diagnosis of coarctation just distal to the left subclavian artery with poststenotic dilatation was confirmed. The coarctation was excised, and the ends of the aorta anastomosed without difficulty. Immediately following the operation, râles were heard in the right side of the chest. Because the patient had received 900 c.c. of blood during operation, a phlebotomy was performed and 275 c.c. of blood were removed. Immediately following this, his heart stopped beating but began again after the injection of 0.5 c.c. of adrenalin.

During the following two hours several small phlebotomies were performed with the removal of an additional 275 c.c. of blood. On three occasions the patient's heart stopped beating but responded to adrenalin. On the fourth occasion, three hours after operation, there was no response to adrenalin and the patient died.

Autopsy.—The heart weighed 250 grams. The left ventricle was markedly dilated, and its wall measured 17 mm. in thickness. The right ventricle was small, measured 3 mm. in thickness, and was not dilated. The aortic valve ring measured 3 cm. in diameter, and there was a subaortic stenosis. The valves were normal. Both lungs were atelectatic.



A. *B.*

Fig. 2 (Case 2).—Coarctation of the aorta and subaortic stenosis. *A*, Congestive heart failure. Moderate cardiac enlargement predominantly in the region of the left ventricle. *B*, Retrograde aortogram showing a coarctation just distal to the origin of the left subclavian artery.

Case 3.—J. W. J., a 38-year-old man, was admitted to the Los Angeles County Hospital on April 4, 1951. He first developed symptoms of heart disease one month prior to admission at which time he complained of shortness of breath and slight swelling of the ankles. Following digitalization his symptoms of congestive failure disappeared, and he was admitted to the hospital for further study.

At the age of 22 he was informed that he had a heart murmur, but nothing was said concerning high blood pressure. At that time, and again ten years before admission, he was refused life insurance because of a "leaky valve". He had never been cyanotic.

The blood pressure was 125/100 mm. Hg. in both arms and 105/95 mm. Hg. in both legs. The cardiac apex was located just within the anterior axillary line. The cardiac rate and rhythm were normal. The aortic second sound was accentuated. A Grade 3 systolic murmur transmitted to the neck vessels was present in the aortic area. There was no thrill. A Grade 3 mitral systolic murmur was heard. No diastolic murmur could be detected. There was no evidence of collateral circulation on physical examination. The lungs were clear. The liver and spleen were not enlarged. No edema was present.

An electrocardiogram showed the pattern of left ventricular hypertrophy.

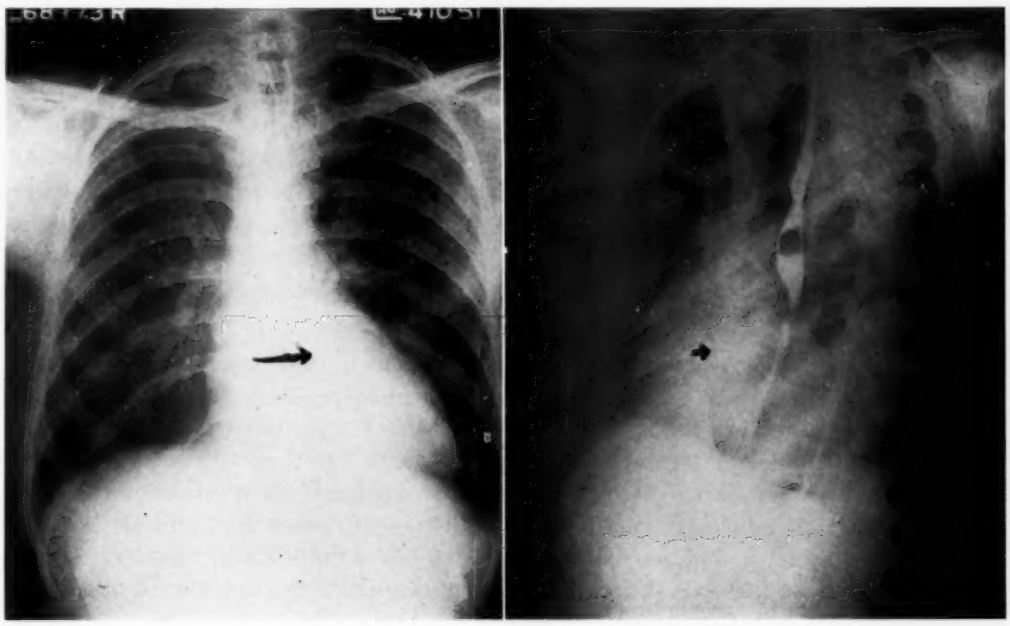
Roentgenograms of the chest showed notching of the ribs posteriorly, left ventricular cardiac enlargement, and a flattened aortic knob, all quite characteristic of coarctation of the aorta. Calcification of the aortic valve was overlooked and was seen only when the films were reviewed after the patient's death (Fig. 3).

On April 13, 1950 the left carotid artery was exposed and a retrograde aortogram was performed. The aorta distal to the left subclavian artery was not visualized and, consequently, neither was the site of coarctation. The internal mammary artery was dilated and quite tortuous

The preoperative diagnosis was coarctation of the aorta with possibly an associated anomaly of the aortic valve.

An operation was performed on April 17, 1951. A coarctation was found just below the origin of the left subclavian artery. The aorta above and below the coarctation showed marked atherosclerosis. The coronary vessels were sclerotic and tortuous, and the heart was markedly enlarged. Dissection of the aorta was difficult because of a periaortitis which involved the subclavian, vertebral, and common carotid arteries. The coarctation was resected, and the ends of the aorta anastomosed without further difficulty.

As soon as the patient was placed in bed, Cheyne-Stokes respiration developed. Following a return to consciousness, he complained of chest pain. Congestive heart failure developed and the patient died the morning after the operation.



A. *B.*

Fig. 3 (Case 3).—Coarctation of the aorta and calcific bicuspid aortic stenosis. A, Postero-anterior and *B*, left oblique views with the usual findings of coarctation: left ventricular enlargement, flattening of the aortic knob, and scalloping of the ribs. Arrows point to aortic valvular calcifications.

Autopsy.—The heart weighed 700 grams. All the chambers were slightly dilated. The wall of the left ventricle measured 19 mm. and that of the right ventricle 4 mm. in thickness.

A recent thrombus was found in the left coronary artery 4 cm. from its origin. Multiple areas of recent hemorrhage and softening were present in the myocardium of the left ventricle and the interventricular septum. The aortic valve measured 4 cm. in diameter. It was bicuspid, markedly calcified, and stenosed. The mitral, pulmonic, and tricuspid valves were normal. The lungs and liver showed evidence of chronic passive congestion.

INCIDENCE OF ASSOCIATED VALVULAR DISEASE INCLUDING SUBAORTIC STENOSIS

Coarctation of the aorta is so frequently accompanied by other congenital cardiac anomalies that Maude Abbott[1] in 1928 after collecting and analyzing 200 cases of coarctation of the adult type, including all adequately described cases in the literature and previously unreported cases from her own and other clinics, stated that "minor anomalies, such as bicuspid aortic valve, anomalous origin of the arteries from the arch, persistent left superior vena cava, defects of the aortic septum, and subaortic stenosis occur relatively so frequent in the adult type as actually to appear to form part of a significant anatomical complex." In 1947 Reifenstein and associates[9] reviewed 104 cases published subsequent to the report of Abbott and made similar observations. While many of the abnormalities such as anomalous vessels are of relatively little clinical significance, the valvular anomalies are of major importance.

Congenital mitral stenosis.—A patient with an interatrial septal defect and congenital mitral stenosis, in whom there was also a minor coarctation of the aorta, was described by Abbott but not included in her series because the coarctation was not of sufficient degree to be considered significant. She also listed one instance of coarctation with "deformity of the mitral valve." No reference is made to a case of clinically significant coarctation associated with congenital mitral stenosis by Reifenstein and associates, nor is it mentioned in any of the other reports reviewed. It is believed that Case 1 is the first such case to be recorded.

Subaortic stenosis.—Six cases of subaortic stenosis complicating coarctation were reported in Abbott's series of 200 cases and two cases by Reifenstein and associates in their series of 104 cases. Grishman and associates,[5] reviewing twenty-three cases of congenital aortic and subaortic stenosis, found one case of subaortic stenosis associated with coarctation. It may be estimated from these reports that subaortic stenosis will be found in 2 to 3 per cent of the patients with coarctation of the aorta. Taussig[10] described a case of coarctation of the aorta combined with subaortic stenosis and aortic insufficiency and stated that this syndrome occurs so frequently as to constitute a definite clinical entity. Case 2 represents an additional instance of this combination of congenital cardiac defects.

Bicuspid aortic valve.—This is the most frequently associated anomaly and was found in 23.5 per cent of Abbott's cases and in a considerably higher proportion, 42.3 per cent of Reifenstein and associates' series. In this latter group, 43 per cent of the bicuspid valves had evidence of previous rheumatic valvulitis, and 27 per cent had evidence of bacterial endocarditis; only 30 per cent were normal.

Rheumatic valvular disease.—Acquired valvular disease was found by Abbott in seventy-three, or 36.5 per cent, of her cases. Reifenstein and associates found that forty-three out of ninety-three of their cases, in which there were adequate post-mortem descriptions of the heart valves, had valvular disease and that nineteen, or 20.4 per cent, were typically rheumatic. These authors state that they "suspect that there is an increased incidence of associated rheumatic heart disease in this group of cases of coarctation but the evidence is not conclusive."

Calcific aortic stenosis.—In addition to the instances of rheumatic valvulitis Reifenstein and associates collected eleven cases of calcific aortic stenosis. Gilbert and associates[4] recently have reported a case of coarctation of the aorta complicated by acquired calcific aortic stenosis. Both Abbott[1] and Clark and Firminger[2] have described a case of calcific aortic stenosis with bisuspid valves. From the literature we have been able to collect fourteen cases of coarctation of the aorta combined with calcific aortic stenosis. Calcified bicuspid aortic valves were described only in the above two cases, in spite of the high incidence of both rheumatic valvulitis and bisuspid aortic valves. Case 3 represents a third instance of biscuspid calcific aortic stenosis complicating coarctation of the aorta. It should be noted that Abbott also described a case of bicuspid aortic stenosis without calcification and that Reifenstein and associates did not comment as to whether or not any of their eleven cases of calcific aortic stenosis had bisucpid valves.

DISCUSSION

In a review of the cause of death of patients in whom surgical correction of coarctation of the aorta has been attempted, it is evident, when the technical failures are eliminated, that those who die postoperatively have coexisting cardiac disease. Gross[7] reported a mortality of 11 per cent in 100 consecutive patients operated upon for coarctation. Six deaths were due to surgical causes such as uncontrollable hemorrhage. The five remaining patients had other associated cardiac disease:

1. Rheumatic mitral stenosis. Congestive failure. Death 6 days after operation.
2. Right bundle branch block. Cardiac failure. Death 4 days after operation.
3. Bicuspid aortic valve with insufficiency. Sudden death 14 hours after operation.
4. Rheumatic mitral stenosis. Congestive failure. Death 4 days after operation.
5. Delayed auriculoventricular conduction. Sudden death as chest was opened.

The only deaths which have occurred in our patients operated upon for coarctation of the aorta are the three cases included in this report. The fact that each had severe valvular disease serves to substantiate Gross's conclusion that: "Operations for correction of a coarctation should be avoided in all persons who have important rheumatic valvular disease, serious conduction system disorders or advanced degrees of aortic insufficiency."

The importance of the valvular lesions is emphasized further by an examination of the causes of death in nonoperative cases. Reifenstein and associates[9] reported that 26 per cent of their patients died from incidental causes. Of the remaining 74 per cent, 23 per cent died from rupture of the aorta, 22 per cent from bacterial endocarditis or aortitis, 11 per cent from an intracranial lesion, and 18 per cent from congestive failure. Abbott reported comparable figures. Those who died from congestive failure are of particular interest in that sixteen of the nineteen patients had evidence of associated chronic valvular disease.

If valvular lesions complicating coarctation, such as occurred in our cases, for example, (1) congenital mitral stenosis, (2) congenital subaortic stenosis, and (3) bicuspid calcific aortic stenosis, are to be recognized preoperatively and unnecessary surgical deaths avoided, then careful attention must be given to the unusual clinical features with which they are associated.

Congestive heart failure in coarctation of the aorta.—Congestive heart failure, present in all three of our cases, does not occur frequently in simple coarctation, and when it does a careful search should be made for an associated valvular lesion. Taussig stated that simple coarctation does not lead to progressive cardiac enlargement. Abbott reported sixty deaths (20 per cent) caused by congestive failure in her series of 200 patients but did not correlate this with the incidence of valvular lesions. Eighteen per cent of the cases of Reifenstein and associates died in congestive failure. Only one of the autopsy records of these nineteen patients contained no mention of other diseases which cause failure and sixteen had chronic valvular disease. These authors felt that their study indicated that the great majority of these patients did not die of congestive failure until some strain, in addition to that due to coarctation, was placed on cardiac function.

Blood pressure in coarctation of the aorta.—The abnormalities of blood pressure in coarctation of the aorta are: (1) upper extremity hypertension, and (2) relative hypotension in the lower extremities. Two of the three cases presented did not fulfill these criteria. Case 2 showed no hypertension of the upper extremities and Case 3 showed elevation of the diastolic pressure in the arms but no elevation of the systolic pressure. It is felt that in both of these cases lack of upper extremity hypertension was due to the combination of a stenotic valvular lesion with coarctation.

Murmurs in coarctation of aorta.—Taussig states ". . . . there is no cardiac mechanism that causes murmurs and thrills, indeed murmurs and thrills over the precordium are the exception rather than the rule." The usual finding is a slight to moderate systolic murmur in the aortic area; diastolic murmurs in the aortic area have been noted on occasions. Systolic murmurs in the mitral area are most unusual.[10]

In two of the three patients studied, evidence was present of organic valvular disease. In Case 1 a mitral diastolic murmur was heard by one observer. In Case 2 a harsh systolic murmur accompanied by a thrill was present over the aortic area. In Case 3 a Grade 3 systolic murmur was transmitted to the neck vessels but no thrill was present.

Electrocardiogram in coarctation of the aorta.—The electrocardiogram in coarctation of the aorta shows left axis deviation with or without the pattern of left ventricular hypertrophy. In Case 1, the patient with mitral stenosis, right axis deviation was present and represented a clue to the recognition of the complicating valvular lesion.

Radiographic findings in coarctation of the aorta.—The uncomplicated case of coarctation of the aorta usually presents radiographic features which are easily recognized and which have been widely described in the literature. On the other hand, an associated valvular lesion may be most difficult to demonstrate.

Angiocardiography is of little value in the average case of mitral stenosis in which there is a typical murmur and when a large left auricle can be demonstrated easily by means of conventional fluoroscopy and radiography. However, angiocardiography may prove valuable when a diagnosis of mitral stenosis cannot be established readily as in Case 1 where specific enlargement of the left auricle

was obscured by generalized cardiac enlargement (Fig. 1,*A* and *B*). Excessive and prolonged opacification of an enlarged left auricle (Fig. 1C) as described by Grishman and associates,[6] was indicative of mitral stenosis, particularly in the presence of murmurs unusual for coarctation and electrocardiographic evidence of right ventricular hypertrophy.

The diagnosis of subaortic stenosis in the presence of coarctation of the aorta is virtually impossible by ordinary radiographic methods. The cardiac contour in subaortic stenosis is normal or, as in coarctation, there may be left ventricular enlargement (Fig. 2). Angiocardiography occasionally may show dilatation of the ascending aorta or rarely the stenosis itself.[3,5] Neither was demonstrated in our case.

Visible calcification of the aortic valve is almost pathognomonic of calcific aortic stenosis, particularly when accompanied by an appropriate murmur, and its demonstration serves to establish the diagnosis as in Case 3 (Fig. 3). Non-calcific aortic stenosis offers the same difficulty in differential diagnosis as does subaortic stenosis.

SUMMARY

1. Three cases of coarctation of the aorta complicated by (a) congenital mitral stenosis, (b) subaortic stenosis, and (c) calcific bicuspid aortic stenosis are reported.

2. The clinical recognition of these associated cardiac lesions is discussed.

3. Each of these patients died during or shortly after surgical correction of the coarctation.

4. It is emphasized that, in the presence of coexisting mitral stenosis, aortic stenosis, or subaortic stenosis, operation for coarctation of the aorta is contraindicated.

REFERENCES

1. Abbott, M. E.: Coarctation of the Aorta of the Adult Type. II. A Statistical Study and Historical Retrospect of 200 Recorded Cases With Autopsy of Stenosis or Obliteration of the Descending Arch in Subjects Above the Age of Two Years, Am. Heart J. **3**:392, 574, 1928.
2. Clark, R. J., and Firminger, H. I.: Coarctation of the Aorta Associated With Adams-Stokes Syndrome, Complete Heart Block and Bicuspid Calcareous Aortic Valve, Report of a Case, New England J. Med. **240**:710, 1949.
3. Dotter, C. T., and Steinberg, I.: Angiocardiography. Ann. Roentgenology, Vol. 20, New York, 1952, Paul B. Hoeber, Inc., pp. 187-189.
4. Gilbert, R. L., Riordan, J. J., and Murphy, J. P.: Coarctation of the Aorta of Adult Type Associated With Acquired Aortic Stenosis, J. Missouri M. A. **47**:333, 1950.
5. Grishman, A., Steinberg, M. F., and Sussman, M. L.: Congenital Aortic and Subaortic Stenosis With Associated Anomalies of the Aorta, M. Clin. North America, **31**:543, 1947.
6. Grishman, A., Sussman, M. L., and Steinberg, M. F.: Angiocardiographic Analysis of the Cardiac Configuration in Rheumatic Mitral Disease, Am. J. Roentgenol. **51**:33, 1944.
7. Gross, R. E.: Coarctation of the Aorta. Surgical Treatment of One Hundred Cases, Circulation **1**:41, 1950.
8. Perlman, L.: Coarctation of the Aorta. Clinical and Roentgenologic Analysis of 13 Cases, Am. Heart J. **28**:24, 1944.
9. Reifenstein, G. H., Levine, S. A., and Gross, R. E.: Coarctation of the Aorta. A Review of 104 Autopsied Cases of the "Adult Type", 2 Years of Age or Older, Am. Heart J. **33**:146, 1947.
10. Taussig, H. B.: Congenital Malformations of the Heart, New York, 1947, Commonwealth Fund, pp. 476, 493-497.

VENTRICULAR STANDSTILL DURING THE INTRAVENOUS PROCAINE AMIDE TREATMENT OF VENTRICULAR TACHYCARDIA

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VENTRICULAR tachycardia is one of the most serious of the arrhythmias encountered in medical practice, and one which requires prompt and intelligent treatment. It is not the problem of the internist alone, but also that of the anesthesiologist[1-3] and the surgeon,[4] who should be prepared to cope with this cardiac emergency.

The treatment of ventricular tachycardia with quinidine was first reported in 1922.[5] Through the years since then it has been established that a substantial portion of cases of ventricular tachycardia treated with quinidine will revert to sinus rhythm. The most recent large series reported was that of Armbrust and Levine in 1950.[6] Of the fifty-seven cases of persistent ventricular tachycardia treated with oral quinidine, forty-six or 80.7 per cent responded favorably. Of those who did not respond, two died, but quinidine was not believed to be a factor in this. Thirty-one patients were given intravenous quinidine for this arrhythmia with success in twenty or 64 per cent of the cases. Two patients were thought to have died from uncontrolled ventricular tachycardia, while four died from quinidine toxicity. The difference in results is due to the more critical condition of the cases selected for intravenous therapy and the fact that some of them had previously failed to respond to oral quinidine.

Numerous instances of undesirable disturbances in cardiac rhythm resulting from quinidine have been reported.[7-17] These were primarily cases of ventricular tachycardia occurring when quinidine was given for auricular fibrillation. The amount of quinidine administered varied, but usually the dosage was high, and often the route was parenteral. Some workers have reported fatal ventricular fibrillation occurring during the intravenous quinidine treatment of patients with ventricular tachycardia and myocardial infarction.[8] Even oral quinidine has precipitated ventricular tachycardia when given for auricular fibrillation,[9] although this is quite rare.

Because of such reports and of others describing convulsions and respiratory arrest from quinidine,[18] many clinicians have been reluctant to use this valuable drug. It should be remembered that the most serious reactions tend to occur when it is given intravenously, and this is now regarded as a hazardous procedure.

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Intravenous quinidine therapy should be used only in critical circumstances, and then with great care.[15,16,19,20] This limits considerably the clinical usefulness of quinidine, although intramuscular preparations are now available.

In the last few years there has been a great deal of investigative work on procaine and its derivatives in the treatment of ectopic rhythms.[1,2,21-24] Procaine increases the threshold for stimulation of cardiac muscle and prolongs the conduction time without decreasing the strength of contraction.[24,25] Its depressant effect is greater than that of quinidine. The earlier clinical studies concerned the beneficial effects of procaine in ventricular tachycardia, and such reports are numerous.[22,24,26,28] Procaine has the disadvantages that it is quickly destroyed in the body, it may have a marked stimulating effect on the central nervous system, and it is not effective orally. Various derivatives of procaine were then tried, and finally procaine amide was found to be the most active and nontoxic substance of the compounds investigated.[26-28]

Procaine amide, or Pronestyl, is active orally or intravenously, and has a more prolonged effect than procaine, without any effect upon the central nervous system.[21] The clinical trials of this drug in ventricular arrhythmias have shown it to be very useful.[25,29,30]

The original studies in 1947 showed that plasma levels of procaine amide are much more sustained than those of procaine, and that gastrointestinal absorption is complete. Dogs were protected against cyclopropane-epinephrine induced ventricular tachycardia for a longer period than by procaine or other procaine derivatives.[31] Three of four patients with prolonged ventricular tachycardia were converted to a sinus rhythm. Later the same investigators found that patients given the drug prophylactically had a smaller incidence of arrhythmias during operations done under cyclopropane anesthesia. More recently it has been shown that experimental ventricular tachycardia produced in dogs by partially tying the anterior descending coronary artery can be terminated by intravenous procaine amide. The results with intravenous procaine were not as good. It is of interest that two of the eight animals treated with procaine amide had a marked hypotension, required very large doses, and finally went into ventricular fibrillation or ventricular standstill and died.[32]

The first series of patients with ventricular tachycardia showed conversion in thirteen of fifteen cases (87 per cent) treated with procaine amide.[33] Another group reported conversion in nine of thirteen patients or 69 per cent.[34] There are also a great many single instances, only a few of which have been reported.[35] The drug has been used prophylactically during operations on the heart or lungs with good results.[4,36]

The toxic side effects of procaine amide have been recognized and include transient hypotension during intravenous administration, and nausea or vomiting with oral medication.[37,38] In addition there are definite electrocardiographic changes: the P-R and Q-T intervals both increase, and the QRS widens.[33,34] Procaine amide seems to be quite safe orally, but most writers recommend that intravenous administration should not be faster than 100 mg. per minute, and that an electrocardiogram should be taken continuously during the injection. Some workers have recently stated that repeated measurements of the blood

pressure are more important than a continuous electrocardiogram, and that the rate of administration should be less than 100 mg. of procaine amide per minute.[38]

It is our purpose here to call attention to a most profound and serious effect of intravenous procaine amide, the precipitation of ventricular arrest or ventricular fibrillation by such therapy. This is the same therapeutic paradox that has been seen with quinidine administration in animals and man. Animal work gave some clues that this might occur, for dogs given repeated small doses of procaine amide intravenously have been observed to die in ventricular fibrillation.[33] Wedd's work on turtle heart strips showed that procaine amide increases the threshold of electrical stimulation and prolongs fiber conduction time.[25] He found the drug to have a marked depressant action in the region of the junctional tissues, and he commented that procaine amide might be dangerous in the presence of disease of the junctional tissues. Several investigators have experienced this event clinically, but few have called attention to it as an important or common occurrence.

Kayden and associates[32] noted that two of their patients with ventricular tachycardia died during the injection of procaine amide and showed that death in one of these cases was due to the development of ventricular fibrillation. This patient received the medication rather rapidly: one gram in two and one-half minutes. Another group of ten patients treated by Berry and his associates[34] with intravenous procaine amide included one who developed ventricular fibrillation and died after receiving a dose of 0.5 Gm. Another patient in this series died similarly during intravenous potassium chloride 40 minutes after he received 1 Gm. of procaine amide intravenously. Still another case has been reported of a patient with an anteroseptal myocardial infarction who received intravenous procaine amide for ventricular tachycardia after quinidine had failed to abolish the arrhythmia. The procaine amide brought about a return of sinus rhythm, but a short while afterwards the patient suddenly died.[39] Cases of cardiac standstill during and shortly after intravenous procaine amide for supraventricular arrhythmias have been reported. One patient with paroxysmal auricular tachycardia repeatedly developed paroxysms of ventricular tachycardia when given procaine amide intravenously.[40] Recently the development of ventricular tachycardia after 0.8 Gm. of procaine amide for auricular fibrillation has been described.[9] Wedd and associates[25] cite instances of ventricular fibrillation and of ventricular standstill in myocardial infarction with ventricular tachycardia treated with oral or parenteral procaine amide. Another recent paper describes ventricular arrest after intravenous procaine amide given to patients with established auriculoventricular dissociation.[41]

In the last ten months we have had the opportunity of observing such a phenomenon in three patients. We do not have accurate figures but believe this to represent about 25 per cent of all patients in a 200-bed general hospital who received intravenous procaine amide during that period, and about 50 per cent or more of those patients who received parenteral procaine amide specifically for ventricular tachycardia. This is a rough index of the incidence of this occurrence, allowing for a short time interval and a small series of cases. Although they were not frequent, these therapeutic catastrophes were so dramatic that we would like to describe them.

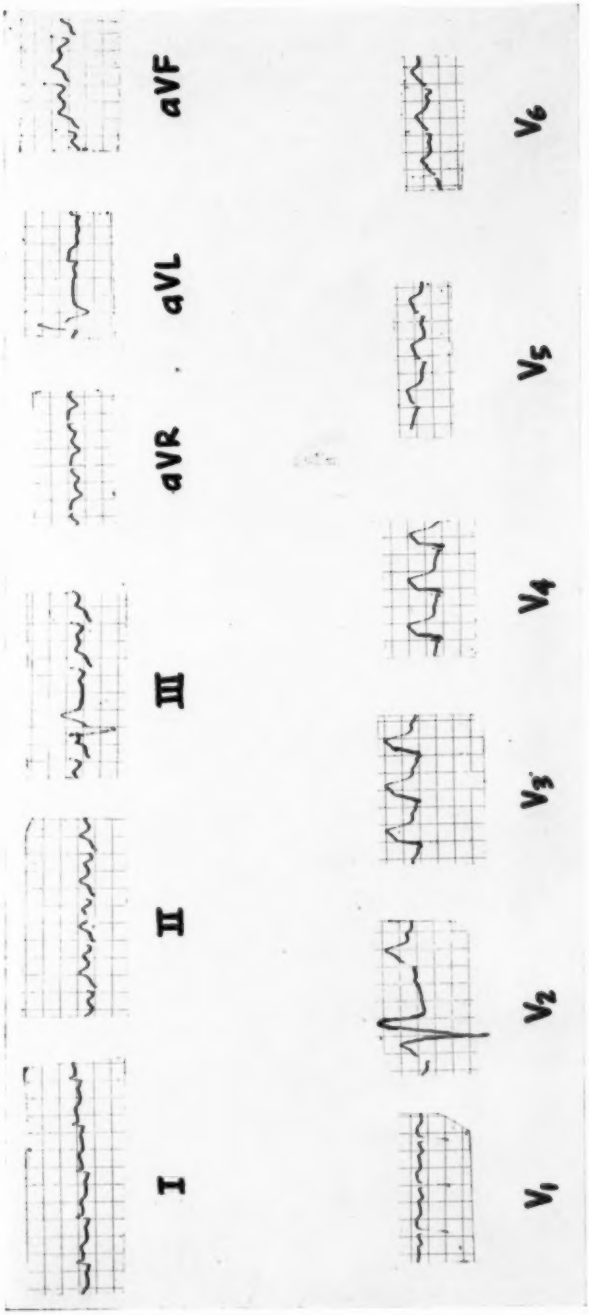

Fig. 1 (Case 1).—Acute infarction.—10/17/51. This tracing was taken about 45 minutes after the onset of severe crushing substernal pain. The Q waves and the S-T segment changes in V_2 to V_5 indicate an acute anteroseptal myocardial infarction with some lateral wall involvement. Ventricular premature beats are seen in Leads *III*, aV_L, and V_2.

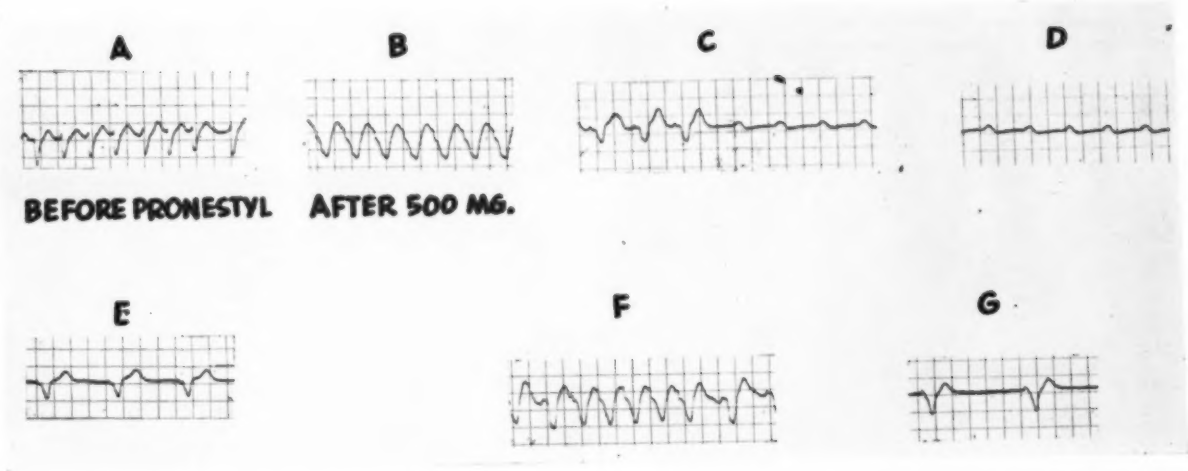

Fig. 2 (Case 1).—During intravenous Pronestyl. *A* shows ventricular tachycardia, and *B* shows widening and smoothing of the complexes from procaine amide therapy. In *C* a sinus rhythm has developed after completion of the intravenous injection of 0.5 Gm. of procaine amide; then the ventricle stops and the auricle continues beating (*C* and *D*). In *E* an idioventricular rhythm has appeared shortly after intracardiac Neo-synephrine. *F* shows a return of ventricular tachycardia several minutes later. In *G* we see the final episode of idioventricular rhythm before terminal ventricular tachycardia and fibrillation occurred.

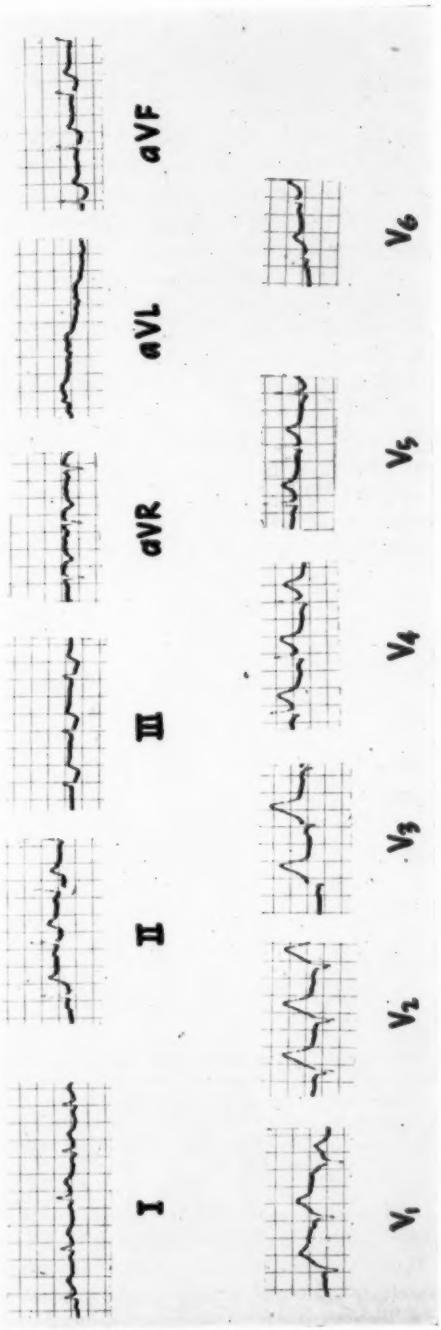

Fig. 3. (Case 2).—Acute myocardial infarction.—8/21/51. This tracing was taken on the admission of Case 2, and shows an acute myocardial infarction fairly well localized to the anteroseptal region. Note that the Q and S-T changes in the precordial leads are present in V_2, V_3, and V_4.

The first patient was a 52-year-old man who was admitted for coronary insufficiency and had a frank coronary occlusion three days later (Oct. 17) while at rest in his hospital bed. The electrocardiogram on that date revealed an anteroseptal myocardial infarction with ventricular premature beats (Fig. 1) and he was given prophylactic procaine amide, 0.75 Gm. every six hours orally. The next afternoon, October 18, he had râles at the bases, a regular pulse of 120, and was dyspneic and orthopneic despite oxygen administration. He was digitalized with 8 c.c. of Cedilanid intravenously at about 5 P.M. The following day, Oct. 19, at 8 A.M. he was in shock, had an irregular pulse of about 120, and appeared much worse. At 8:30 A.M. an electrocardiogram revealed ventricular tachycardia at a rate of 140. At about 9 A.M. he was given 0.5 Gm. of procaine amide intravenously with no immediate change in his rhythm, but a half hour later sinus rhythm returned. He was given 0.1 Gm. of digitalis leaf at 10 A.M. on the same day.

The next morning, Oct. 20, he again had ventricular tachycardia and was given 0.5 Gm. of procaine amide very slowly by vein. As the injection was completed he developed ventricular standstill, but the auricles continued beating (Fig. 2, *C*); he became comatose at this time. He was given Neo-synephrine hydrochloride 0.5 mg. intracardially, and then developed auriculoventricular dissociation with idioventricular rhythm (Fig. 2, *E*), and finally returned to ventricular tachycardia. About thirty minutes later, never having regained consciousness, he developed fulminating pulmonary edema and died.

The second patient was a 47-year-old man who was admitted twelve hours after the onset of severe substernal pain. An electrocardiogram on admission showed an acute myocardial infarction and suggested involvement of the septum (Fig. 3). He did poorly: he had persistent pain, tachycardia, showed a leucocytosis, and ran a temperature of 102° F. On his third day in the hospital he was worse, and he had a pulse of 190 which was quite irregular. An electrocardiogram

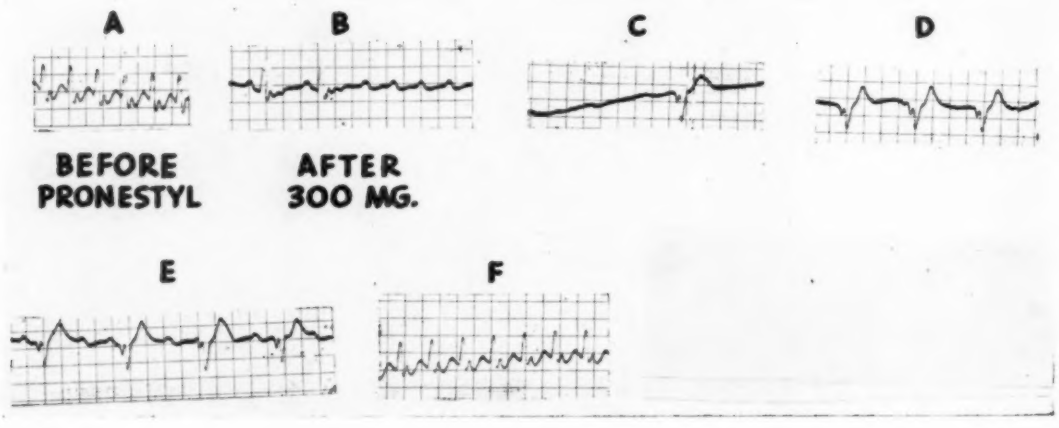

Fig. 4 (Case 2).—Intravenous Pronestyl. This shows the sequence of events in Case 2 when procaine amide was given intravenously. *A* shows ventricular tachycardia, and *B* demonstrates the change from sinus rhythm to ventricular arrest. In *C* there is a period of complete cardiac arrest, with the first return of ventricular activity at the end of the strip. *D* shows an idioventricular rhythm a few minutes later. *E* illustrates the complete A-V dissociation and *F* the return of ventricular tachycardia.

then showed ventricular tachycardia. He was given 0.3 Gm. of procaine amide intravenously over a five minute period with a continuous electrocardiogram (Fig. 4). After this he developed ventricular arrest but auricular activity continued (Fig. 4, *B*). Concomitant with this he had a grand mal seizure and became comatose. Then there was a ten-second period of complete cardiac arrest (Fig. 4, *C*). After this an idioventricular rhythm slowly appeared, with the rate of the ventricle about one-half that of the auricle. Following this there was a return of ventricular tachycardia after about five minutes (Fig. 4, *F*). He remained unconscious and in profound shock, and despite supportive measures died one and one-half hours later.

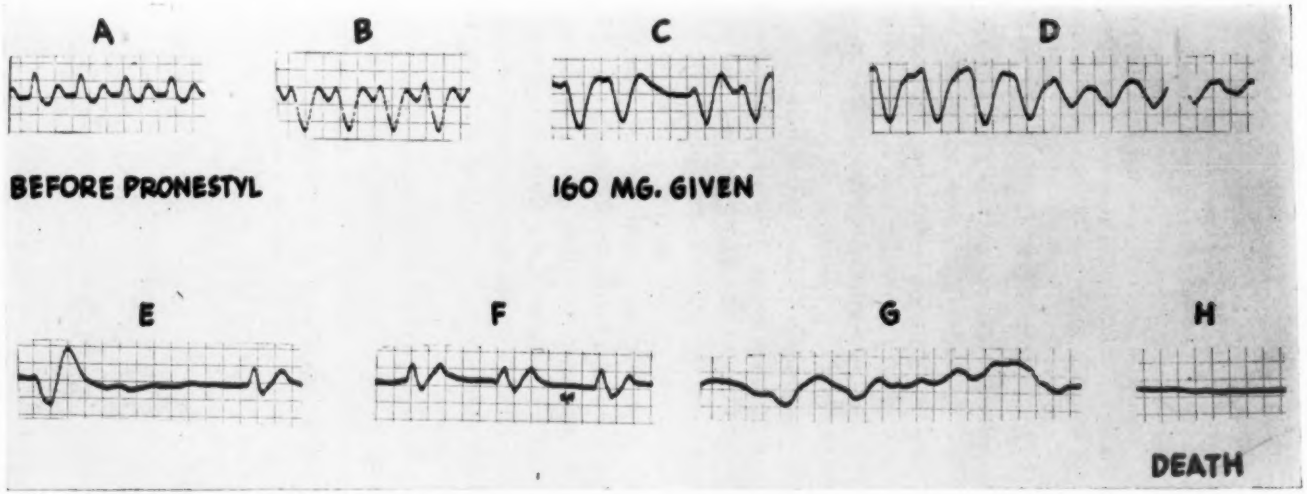

Fig. 5 (Case 3).—Fatal intravenous Pronestyl. *A* shows ventricular tachycardia in Case 3, and *B* shows the electrocardiographic changes from the procaine amide just injected. In *C* the procaine amide effect is increasing, and *D* shows ventricular flutter-fibrillation. This was only a few minutes after a total of 0.16 Gm. of procaine amide was given in four minutes intravenously. *E* shows a period of cardiac arrest, then an idioventricular rhythm in *F*. *G*, taken a few minutes later, demonstrates ventricular fibrillation followed shortly in *H* by final cardiac arrest.

Autopsies, done on these two patients, showed marked coronary atherosclerosis, anteroseptal myocardial infarction, pulmonary edema, and visceral congestion. All of the septum was infarcted in the first case, only the mid-portion in the second.

The third case was that of a 55-year-old man (Fig. 5) with rapidly progressive hepatic insufficiency from cirrhosis who developed an *E. coli* bacteremia. He improved temporarily on antibiotics and Corticotropin, then rapidly went into hepatic failure. During this period he was found one morning to be in shock with a pulse of 130. An electrocardiogram showed ventricular tachycardia. There was no prior history of heart disease, and a previous electrocardiogram was normal. He was given 0.16 Gm. of procaine amide intravenously over a four-minute period and almost immediately thereafter developed ventricular flutter-fibrillation (Fig. 5, *D*), then an idioventricular rhythm. This was followed in a few minutes by recurrent ventricular tachycardia, then cardiac standstill for 2.5 seconds (Fig. 5, *E*). After this he went into ventricular fibrillation and died (Fig. 5, *G*, *H*).

DISCUSSION

The mechanism for this unfortunate sequence of events as seen in these cases can only be conjectured. Quinidine and procaine amide are both cardiac depressants, having an effect on the ventricles, auricles, and junctional tissues in varying degree. In septal infarction the mechanism can be imagined relatively easily. The junctional tissues are diseased, the ventricle is irritable and goes into tachycardia. When sudden marked depression of the ventricle and of the junctional tissue is effected by intravenous procaine amide, the ventricle either fibrillates or stops because there is no pacemaker to drive it. Theoretically, it seems likely that so many muscle bundles in the ventricle become depressed that the idioventricular pacemaker ceases to function and the ventricle contracts irregularly and incoordinately in various areas (fibrillation). If the myocardial depression is very great, the ventricle may stop completely. The continuation of auricular systole in two of the cases lends strong support to this line of reasoning. It seems quite significant that auricular systole with ventricular arrest occurred in both patients with septal infarctions, yet not in the third who had no damaged junctional tissue. This identical phenomenon has recently been described by Schwartz and his co-workers,[41] studying patients with established auriculoventricular dissociation.

In Case 3 we might postulate several possible mechanisms for the rapidly fatal untoward response to procaine amide. In this patient the drug might have unduly depressed the supraventricular pacemakers so that complete cardiac arrest occurred when the ventricular rhythm was terminated. Indeed, Schwartz's group[41] has demonstrated such depression of the supraventricular pacemakers by procaine amide. The cirrhosis may have been an important factor, since patients with hepatic insufficiency do not detoxify drugs properly and often have untoward reactions to ordinarily harmless medications. This might be the most important factor in this patient's death from procaine amide.

From reviewing the experiences of others and analyzing our own cases, we believe that certain conclusions can be drawn in regard to intravenous procaine amide therapy.

1. Procaine amide should never be given intravenously without clear-cut clinical and electrocardiographic indications. The single most important indication is failure of a serious arrhythmia to respond to oral quinidine or procaine amide.
2. An electrocardiogram should be taken continuously during intravenous procaine amide and for ten to fifteen minutes afterwards. Then tracings should be made every five to ten minutes for one hour.

3. The blood pressure should be measured frequently during treatment and the injection interrupted or stopped if there is a fall of 15 mm. or more.
4. Procaine amide should not be given intravenously at rates greater than 50 mg. per minute. The solution should be diluted with saline to make very slow administration easier.
5. Unusually great care should be used in giving this drug parenterally to patients with coronary disease. Intravenous procaine amide is probably contraindicated in septal infarction, in bundle branch block, and in the presence of any substantial amount of auriculoventricular block.
6. Prophylactic administration of procaine amide during operation on patients with cardiac lesions should be done very cautiously and the patient followed closely with blood pressures and a continuous electrocardiogram.
7. Syringes, intracardiac needles, and pressor drugs should be at the bedside when procaine amide is given parenterally, but they should be used only for electrocardiographically proved cardiac arrest.

In conclusion we can see that further clinical experience with a relatively new drug has demonstrated serious side effects. The drug remains a useful one, and we should not discard it, but only increase the care with which we select patients and administer the preparation to them.

SUMMARY

1. The literature on the treatment of ventricular tachycardia with quinidine and with procaine amide is briefly reviewed.

2. Three cases of serious cardiac depression occurring with procaine amide properly administered intravenously are reported. One of these patients died immediately after the injection.

3. The possible mechanism of this reaction is discussed.

4. Recommendations are made regarding the use of intravenous procaine amide. The drug should probably not be given by this route in septal infarction, bundle branch block, and auriculoventricular block.

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REFERENCES

1. Burstein, C. L., Marangoni, B. A., DeGraff, A. C., and Rovenstine, E. A.: Protecting Action of Procaine Against Ventricular Fibrillation, Anesthesiology **1**:167, 1940.
2. Burstein, C. L.: Treatment of Acute Arrhythmias During Anesthesia by Intravenous Procaine, Anesthesiology **7**:113, 1946.
3. Marangoni, B. A., Burstein, C. L., and Rovenstine, E. A.: Protecting Action of Chemicals Related to Procaine on Ventricular Fibrillation During Cyclopropane Anesthesia, Proc. Soc. Exper. Biol. & Med. **44**:594, 1940.
4. Joseph, S. I., Helrich, M., Kayden, H. J., Orkin, L. R., and Rovenstine, E. A.: Procaine Amide for Prophylaxis and Therapy of Cardiac Arrhythmias Occurring During Thoracic Surgery, Surg., Gynec. & Obst. **93**:75, 1951.
5. Scott, R. W.: Observations on a Case of Ventricular Tachycardia With Retrograde Conduction, Heart **9**:297, 1922.
6. Armbrust, C. A., Jr., and Levine, S. A.: Paroxysmal Ventricular Tachycardia: A Study of 107 Cases, Circulation **1**:28, 1950.
7. Binder, M. J., and Rosove, L.: Paroxysmal Ventricular Tachycardia and Fibrillation Due to Quinidine, Am. J. Med. **12**:491, 1952.
8. Rakov, H. L.: Ventricular Fibrillation in Acute Coronary Thrombosis During the Intravenous Administration of Quinidine Sulfate: Report of a Fatal Case, Ann. Int. Med. **16**:571, 1942.
9. Schreiner, G. E., and Kelley, R. T.: Ventricular Tachycardia After Pronestyl and Quinidine, Am. Heart J. **43**:749, 1952.

10. Levy, R. L.: Clinical Toxicity of Quinidine, J. A. M. A. **78**:1919, 1922.
11. Levy, R. L.: Clinical Studies on Quinidine: Alterations in Cardiac Mechanism After Administration of Quinidine to Patients With Auricular Fibrillation With Consideration of Certain Toxic Effects of the Drug, Arch. Int. Med. **30**:451, 1922.
12. Levy, R. L.: Some Results of Quinidine in Auricular Fibrillation, New York State J. Med. **22**:276, 1922.
13. Kerr, W. J., and Bender, W. L.: Paroxysmal Ventricular Tachycardia With Cardiac Recovery in Auricular Fibrillation and Complete Heart Block While Under Quinidine Sulfate Therapy, Heart **9**:269, 1922.
14. Lewis, T., Drury, A. N., Wedd, A. M., and Iliescu, C. C.: Observations Upon the Actions of Certain Drugs on Fibrillation of the Auricles, Heart **9**:207, 1922.
15. DiPalma, J. R., and Schultz, J. E.: Antifibrillatory Drugs, Medicine **29**:123, 1950.
16. Hepburn, J., and Rukert, H. E.: The Use of Quinidine Intravenously in Ventricular Tachycardia, Am. Heart J. **14**:620, 1937.
17. Schwartz, S. P., and Jezer, A.: The Action of Quinine and Quinidine on Patients With Transient Ventricular Fibrillation, Am. Heart J. **9**:792, 1934.
18. Harris, A. S., Estandia, A., Ford, T. J., and Tillotson, R. F.: Quinidine Lactate and Gluconate in the Suppression of Ectopic Ventricular Tachycardia Associated With Myocardial Infarction, Circulation **4**:522, 1951.
19. Sprague, H. B.: The Treatment of Cardiac Arrhythmias, Post-Graduate Course on Heart Disease, Rochester (N. Y.) Academy of Medicine, April, 1950.
20. Williams, C., and Ellis, L.: Ventricular Tachycardia: An Analysis of 36 Cases, Arch. Int. Med. **71**:137, 1943.
21. Newman, P. J., and Clark, B. B.: Comparative Study of the Pharmacologic Properties of Procaine and Procaine Amide, Federation Proc. **9**:304, 1950.
22. Long, J. H., Oppenheimer, M. J., Webster, M. R., and Durant, T. M.: The Effect of Intravenous Procaine on the Heart, Anesthesiology **10**:406, 1949.
23. Mark, L. C., Lott, W. A., Cooper, J. R., and Brodie, B. B.: Studies on Diethylaminoethanol, J. Pharmacol. & Exper. Therap. **98**:405, 1950.
24. Wedd, A. M., and Blair, H. A.: The Action of Procaine on the Heart, Anesthesiology **12**:261, 1951.
25. Wedd, A. M., Blair, H. A., and Warner, R. S.: The Action of Procaine Amide on the Heart, Am. Heart J. **42**:399, 1951.
26. Papper, E. M., Brodie, B. B., Lief, P. A., and Rovenstine, E. A.: Studies on Pharmacological Properties of Procaine and Diethylaminoethanol, New York State J. Med. **48**:1711, 1948.
27. Rosenberg, B., Kayden, H. J., Lief, P. A., Mark, L. C., Steele, J. M., and Brodie, B. B.: Studies on Diethylaminoethanol: Physiological Disposition and Action in Cardiac Arrhythmias, J. Pharmacol. & Exper. Therap. **95**:18, 1949.
28. Rovenstine, E. A., and Papper, E. M.: The Therapeutic Role of Procaine and Its Derivatives, Bull. New York Acad. Med. **25**:298, 1949.
29. Schaffer, A. I.: Procaine Amide Compared With Quinidine as a Therapy for Arrhythmias, Am. Heart J. **42**:597, 1951.
30. Kinsman, J. M., Clay, H. L., Coe, W. S., and Best, M. M.: Procaine Amide in the Treatment of Disorders of Cardiac Rhythm, Kentucky M. J. **48**:509, 1950.
31. Mark, L. C., Berlin, I., Kayden, H. J., Rovenstine, E. A., Steele, J. M., and Brodie, B. B.: The Action of Procaine Amide on Ventricular Arrhythmias, J. Pharmacol. & Exper. Therap. **98**:21, 1950.
32. Harris, A. S., Estandia, A., Ford, T. J., Jr., Smith, H. T., Olsen, R. W., and Tillotson, R. F.: The Effects of Intravenous Procaine and Procaine Amide (Pronestyl) Upon Ectopic Ventricular Tachycardia Accompanying Acute Myocardial Infarction, Circulation **5**:551, 1952.
33. Kayden, H. J., Steele, J. M., Mark, L. C., and Brodie, B. B.: The Use of Procaine Amide in Cardiac Arrhythmias, Circulation **4**:13, 1951.
34. Berry, K., Garrett, E. L., Bellett, S., and Gefter, W. I.: The Use of Pronestyl in Treatment of Ectopic Rhythms: 98 Episodes in 78 Patients, Am. J. Med. **11**:431, 1951.
35. Hanenson, I. B., Kayden, H. J., and Messinger, W. J.: Recurrent Ventricular Tachycardia Treated With Procaine Amide, Am. Heart J. **43**:293, 1952.
36. Epstein, M. A.: Unpublished Observations, 1952.
37. Schaffer, A. I., Blumenfeld, S., Pitman, E. R., and Dix, J. H.: Procaine Amide: Its Effect on Auricular Arrhythmias, Am. Heart J. **42**:115, 1951.
38. Stearns, N. S., Callahan, E. J., III, and Ellis, L. B.: Value and Hazards of Intravenous Procaine Amide Therapy, J. A. M. A. **148**:360, 1952.
39. Irvin, C. W., Jr., and Cutts, F. B.: Ventricular Tachycardia: Report of a Case in Which Pronestyl was Effectively Used After Failure With Quinidine, J. A. M. A. **146**:1282, 1951.
40. McCord, M. C., and Taguchi, J. T.: A Study of the Effect of Procaine Amide Hydrochloride in Supraventricular Arrhythmias, Circulation **4**:387, 1951.
41. Schwartz, S. P., Hallinger, L., and Imperialli, A.: Transient Ventricular Fibrillation. IV. The Effects of Procaine Amide on Patients With Transient Ventricular Fibrillation During Established Auriculoventricular Dissociation, Circulation **6**:193, 1952.

THE ACTION OF A NEW ORAL PREPARATION OF DIGITALIS, ACETYLDIGOXIN

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ACETYLDIGOXIN can be derived from lanatoside C by splitting off the glucose molecule. It is thus intermediate between lanatoside C and digoxin. Because there is evidence indicating that acetyldigoxin is more completely absorbed from the intestinal tract than digoxin, as discussed below, the former drug was subjected to clinical trial. There has been no previous clinical study of acetyldigoxin.

METHOD

Twenty-six patients with heart disease due to rheumatic fever, hypertension, or arteriosclerosis were treated with acetyldigoxin. Thyrotoxicosis was an additional factor in four patients. Twenty-three were in frank congestive failure. The rhythmic mechanisms were as follows: chronic auricular fibrillation, 20; paroxysmal auricular fibrillation, 3; supraventricular tachycardia, 1; frequent ventricular premature systoles, 1; normal sinus rhythm, 1.

The effects of single doses of 2 and 3 mg. of acetyldigoxin orally were observed in undigitalized patients over periods of six hours to two weeks. Subsequent doses to achieve and maintain a state of digitalization were determined according to the patients' clinical responses rather than by a predetermined schedule. Patients were considered to be undigitalized after three weeks freedom from digitalis leaf or Digitoxin, 2 weeks after cessation of digoxin, and when their clinical states supported this belief (increasing heart failure, sustained tachycardia). The action of single doses varying from 0.5 to 2.0 mg. was also observed in partially digitalized patients.

The apical heart rate was counted several times a day during control periods, and hourly during acute phases of digitalization. Conditions, such as physical activity and adjuvant therapy, were kept constant throughout control and treatment periods. Electrocardiograms were made at irregular intervals before and after administration of the drug, and venous pressures were measured with the Burch phlebomanometer.

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RESULTS

1. *Effects of a single dose on undigitalized patients.*—These patients had control apical rates of 92 per minute in one case, and from 118 to 160 in the others. At the peak of action, the rates were most often in the 70 to 80 range. In seven instances repetition of the initial dose, at the time dissipation was judged to be complete, was followed by responses similar to the original ones. The data are summarized in Table I and exemplified in Figs. 1 and 2.

TABLE I. ACTION OF SINGLE DOSES OF ACETYLDIGOXIN IN UNDIGITALIZED PATIENTS WITH AURICULAR FIBRILLATION

DOSE	TIME FOR 10% FALL IN RATE	TIME FOR 20% FALL IN RATE	PEAK OF ACTION	DISSIPATION	NO. OF TRIALS
2 mg.	1-9 hrs. mean, 3.3	4-10 hrs. mean, 5	4-12 hrs. mean, 9	8-12 days mean, 10	13 (10 patients)
3 mg.	1-4 hrs. mean, 2.1	1-7 hrs. mean, 4	6-12 hrs. mean, 7	6-12 days mean, 9	16 (11 patients)

2. *Effects of a single dose on partially digitalized patients.*—There were fourteen trials in eight patients, whose apical rates ranged from 78 to 140 per minute. A 20 per cent fall in rate occurred in 4 to 12 hours, with a mean of 6 hours. Maximal effects on the rate appeared in the same time range, with a mean time of 7 hours. The doses were 0.5 to 2.0 mg.

3. *Absence of effect.*—In two cases there was no significant slowing nor other observed effect after a 3 mg. dose. Both patients died within 24 hours, and at autopsy both were found to have metastatic neoplastic involvement of the heart.

4. *Maintenance of digitalization.*—Satisfactory daily maintenance doses were found to be between 0.4 and 0.7 mg. Daily maintenance doses of 0.8 to 1.0 mg. generally resulted in toxicity after 3 to 9 days, even when given in divided fashion.

5. *Toxicity.*—Toxic manifestations were mild, consisting of nausea in two cases, vomiting in two, occasional ventricular premature systoles in one, and yellow vision in one. These ill effects disappeared within 24 hours after the drug was withdrawn or the dose sharply reduced. No toxicity was encountered after a single dose of 3 mg. or less in an undigitalized patient.

6. *Electrocardiographic observations.*—There were no abrupt or unusual changes in the RS-T segments or T waves. RS-T segmental deviation and lowering of T waves were not uniformly found after administration of the drug. The use of the Q-T interval to determine onset of digitalis effect was abandoned because of the difficulty of making precise measurements in the presence of auricular fibrillation. In the patient with frequent ventricular premature systoles (33 out of every 99 beats) a 3 mg. dose reduced their frequency so that in 4 hours there were 36 among 176 beats, and in 11 hours only 2 among 216 beats. Their frequency then increased for the next 20 hours, until every fourth beat was premature.

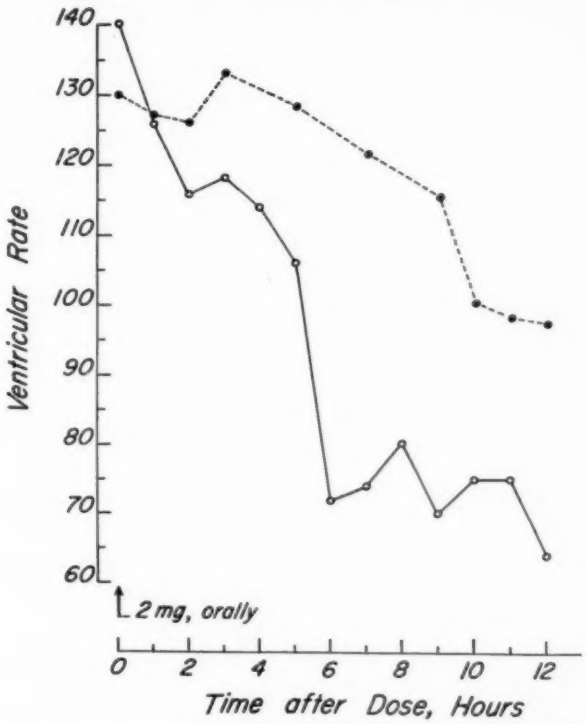

Fig. 1. —Examples of a poor response (patient with thyrotoxicosis) and a rapid response to a single dose of 2 mg.

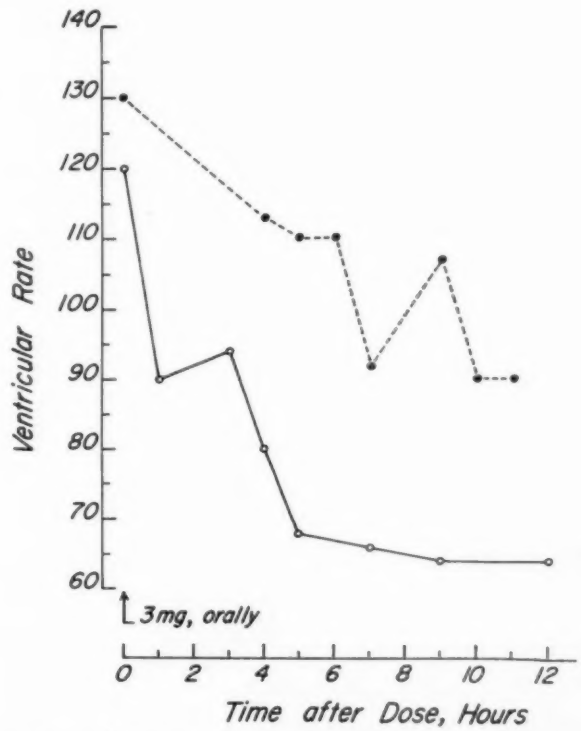

Fig. 2.—Examples of a poor response (patient with thyrotoxicosis) and a rapid response to a single dose of 3 mg.

7. *Venous pressure.*—Significant changes were not observed in the first few hours after administration of the drug but were seen later when improvement in the degree of heart failure was accompanied by lowering of the venous pressure.

DISCUSSION

Bio-assay of acetyldigoxin by the Hatcher method, infusing a 1:50,000 solution intravenously at a rate of 1 c.c. per minute, yields a cat unit value of 0.383 mg. per kg.[1] For the purpose of studying enteral absorption of the drug, intraduodenal infusion of the same dilution but at a rate of 0.25 c.c. per minute has been employed. This gave a cat unit value of 0.494 mg. per kg. Intravenous infusion at the same slow rate gave a cat unit value of 0.275 mg. per kg.[1] These figures indicate that 56 per cent of the drug is enterally absorbed. By this method it has been found that enteral absorption of other preparations is as follows: digoxin, 43 per cent; lanatoside C, 29 per cent; Digitaline-Nativelle, 86 per cent; and Digitoxin-Sandoz, 75 per cent. It would appear from these figures that the oral absorption of acetyldigoxin might be sufficiently greater than that of digoxin to justify our anticipation that the newer drug might act more potently.

Publications, dealing with digitalis action clinically, generally mention no exact criteria for establishing the latent period (time of onset of effects). Indeed, it is most difficult to be precise in this matter because of the gradual onset of action after oral administration and because of spontaneous variations in the ventricular rate of patients with auricular fibrillation. We have arbitrarily selected as criteria for establishing the latent period the time of occurrence of a 10 per cent fall and a 20 per cent fall in ventricular rate. This at least permits comparison with published reports which contain data on heart rates.

The average latent period of acetyldigoxin is 2 to 5 hours, depending upon the size of the dose used and the degree of slowing accepted as the criterion of onset of action. The drug exerts its full effect about 7 to 9 hours after administration; and the clinical effects wear off 9 or 10 days after a single dose of 2 or 3 mg. All these characteristics are much the same as those of digoxin.[2-6] The type and duration of toxicity are also very similar to those seen with digoxin.[7] Thus, despite the experimental evidence of significantly greater enteral absorption of acetyldigoxin, the newer drug does not appear to be particularly different from digoxin in its clinical action.

On the basis of our experience we would recommend for initial digitalization a single dose of 2 mg., followed by 0.5 mg. doses at intervals of 6 to 8 hours until a satisfactory effect is achieved. Maintenance can be accomplished by daily doses of 0.4 to 0.7 mg. These figures are given only as a guide, since digitalization is an individualized procedure for each patient.

Finally, it may not be inappropriate to comment upon an incidental finding which is probably encountered in any study involving patients with auricular fibrillation; that is, the variability of ventricular rate in some cases. It is well known that during auricular fibrillation the ventricles may accelerate greatly on exercise, and that this effect is diminished by digitalis. A striking feature of this acceleration is the abruptness with which it occurs, even in digitalized patients.[8]

In our series there were seven patients who exhibited abrupt increases in ventricular rate by 20 to 40 beats per minute. However, these increases occurred as a consequence of emotional stimuli such as the entrance of visitors, demonstration to postgraduate students, and other relatively minor disturbances. These rapid rates generally subsided within a few minutes, though they occasionally lasted up to an hour. Digitalization did not prevent these responses or their abruptness, but did lessen the extent of acceleration. We believe that such events are fairly common clinical experience. They must be looked for and properly evaluated in clinical studies involving the heart rates of patients with auricular fibrillation.

SUMMARY AND CONCLUSIONS

1. Acetyldigoxin was given orally to twenty-six patients, of whom twenty-three had auricular fibrillation.

2. The effects of a single full dose became manifest in about two hours, and maximal in about seven hours. Dissipation was complete in about nine days.

3. Despite experimental evidence of greater absorption of acetyldigoxin, the drug did not appear to differ from digoxin in its clinical action.

4. The frequent occurrence of abrupt acceleration of the ventricles in patients with auricular fibrillation was stressed.

REFERENCES

1. Rothlin, E.: Personal communication from Sandoz Pharmacological Laboratories.
2. Wayne, E. J.: Clinical Observations on 2 Pure Glucosides of Digitalis, Digoxin and Digitalinum Verum, Clin. Sc. **1**:63, 1933.
3. Schwab, E. H.: Clinical Observations on a Pure Glucoside of Digitalis Lanata, Digoxin, Tex. State J. Med. **35**:619, 1940.
4. Hanlon, L. W., Gold, H., Modell, W., Benton, J. G., and Cotlove, E. W.: Absorption of Digoxin in Man, Fed. Proc. **6**:334, 1947.
5. Batterman, R. C., and DeGraff, A. C.: Studies in the Rate of Dissipation of Digoxin in Man, Federation Proc. **4**:112, 1945.
6. Evans, W., Dick, P., and Evans, B.: Rapid Digitalization, Brit. Heart J. **10**:103, 1948.
7. Batterman, R. C., and DeGraff, A. C.: Comparative Study on the Use of the Purified Digitalis Glycosides, Digoxin, Digitoxin, and Lanatoside C, For the Management of Ambulatory Patients With Congestive Heart Failure, Am. Heart J. **34**:663, 1947.
8. Knox, J. A. C.: The Heart Rate With Exercise in Patients With Auricular Fibrillation, Brit. Heart J. **11**:119, 1949.

NEW DEVICE FOR OBJECTIVE AUSCULTATION OF THE HEART: PERMANENT AUDIBLE AND VISUAL RECORD OF THE HEART ACOUSTICS

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ALTHOUGH auscultation is known to be a most important part of clinical examination of the heart, the findings are often controversial and the diagnosis questionable. Each physician listens to the patient's heart individually; the examination is, therefore, subjective. The lack of identity and of precision in the findings is due to the imperfect senses of the clinician. Moreover, once the examination of the heart is finished, and the patient has left, no discussion, comparison, or study of the findings is possible, inasmuch as no record of the heart acoustics is available for audible reproduction.

Direct auscultation of the heart was already known by Hippocrates. Until 1816 physicians used the ear without mechanical aid. Since the invention of the stethoscope by Laënnec, this instrument has been helpful in focusing and amplifying the sounds and murmurs of the heart. Recording of heart beats and sounds is also an old and known procedure; however, the visual graph and the audible sound were not combined in one record. Other developments have included the electrostethograph which provides a tracing of the heart sounds and murmurs, and attempts have been made to record heart sounds and murmurs on phonographic discs and other media. Another apparatus, the cardioscope, based on cathode ray tubes has been used in clinical evaluation of heart conditions which gives only a fluorescent image of the heart beats, sounds, and murmurs. These visual waves disappear instantly. Despite these many devices, an objective method of auscultation, together with a permanent audible and visual record, has not been achieved satisfactorily to date. A device for simultaneous recording of heart sounds, beats, and murmurs for visual and audible reproduction has been developed which might improve the ordinary methods used in physical diagnosis.

TECHNIQUE

In order to register simultaneously the heart acoustics for visual and audible reproduction, three known instruments (eventually to be combined into one unit) are used: the electrocardiograph, the phonostethograph, and the electromagnetic tape recorder (Fig. 1).

While the limb and chest leads *1* pick up the electrical waves of the heart beats, and finally transmit the magnified waves upon a moving medium *2*, the microphone *4* simultaneously picks up the heart sounds and murmurs. These are first carried to the same moving medium *2* for visual recording of the sound,

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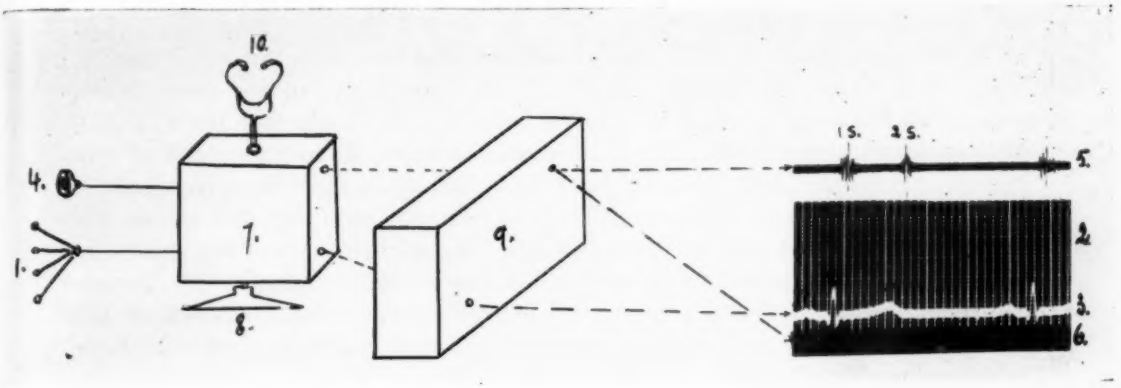

Fig. 1.—Audio-viso cardiograph:

1. Limb and precordial leads (electrocardiogram).
2. Moving medium, partly photosensitized, partly electromagnetized.
3. Electrocardiogram.
4. Microphone.
5. Electrophonostethogram.
6. Electromagnetic tape for audible reproduction of the heart acoustics.
7. Amplifier.
8. Loud speaker.
9. Galvanometer.
10. Stethoscope.

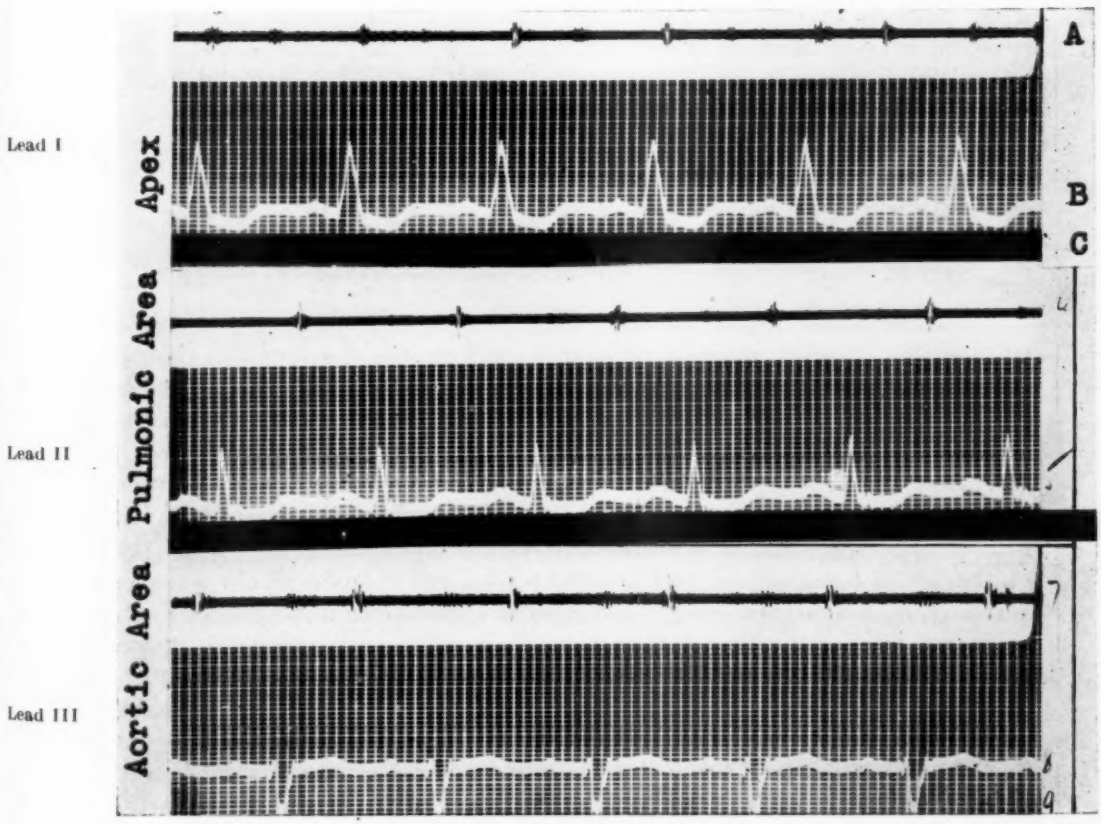

Fig. 2.—Audio-viso cardiogram showing the simultaneous presentation of heart acoustics: *A*, stethogram; *B*, electrocardiogram; *C*, sound tape (electromagnetic sound tape).

which is the known electrostethogram *5*; the same sounds and murmurs picked up by the microphone *4* are simultaneously recorded on a sound magnetic tape *6*. Thus we have a simultaneous visual and aural recording of the heart beats, sounds, and murmurs which can be called an audio-visocardiogram (AVCG). This permanent record (Fig. 2) can be studied, compared, and discussed at will, any time, anywhere. It can be kept in file or shipped anywhere to be examined by a physician who did not actually examine the patient. By this means, the sounds are less distorted, the tape giving higher fidelity while reproducing the recording, than the phonographic disc. The sound tape, attached to the permanent record in the form of a loop, can be removed at will and played back on any conventional recording machine, running at the same speed as when it was obtained originally.

LIMITATIONS AND ADVANTAGES

It is obvious that we do not hear exactly the heart beats, sounds, and murmurs just as they are produced within the chest. This is due to faulty transmission through different media within the chest, and receptive media outside the chest, the stethoscope, and the ear itself. The same limitations can be applied to the amplifying system and the loud speaker. There are still some imperfections in the reproduction systems, but there is hope that distortions and extra noises will be eliminated completely in the future. On the other hand, because of the high sensitized microphone and the amplification, the electromagnetic system may occasionally pick up and reproduce heart sounds and murmurs otherwise not heard by the human ear, namely some high-pitched musical murmurs, split sounds, some gallop rhythms, and third and fourth sounds, crescendi and diminuendi, some high-frequency, low-intensity diastolic murmurs, and so forth. Finally, some murmurs or other cardiac abnormalities might be detected earlier than by the usual means.

APPLICATIONS

The described apparatus may have multiple applications in medicine and surgery. The permanent visual and audible record will enable the physician to follow a given disease step by step. In many instances, questionable murmurs become clarified. Any eventual change in the quality of a sound or murmur can be added and compared instantly with those previously recorded. For instance, in rheumatic mitral stenosis, all the characteristics of the auscultation may be recorded, later on the spreading to other valves, or improvement with disappearance of the murmur and restitution of the normal heart sounds can be added subsequently to the same record and reproduced chronologically. Similarly, such a method might have possible applications in surgery of the heart or its vessels, as in the ligation or section of a patent ductus arteriosus, an anastomosis in a pulmonary stenosis, or a dilatation of a stenotic mitral valve. In these and other aspects of cardiac surgery, the acoustic record would enable an immediate postoperative evaluation of the procedure. In obstetrics, any change during labor of the fetal beats could be recorded and appropriate steps taken in case of emergency. The described method and device might prove useful for

teaching purposes, in clinics, in induction centers, factories, insurance companies, legal medicine and so forth, those situations in which a permanent record might prove of value.

CONCLUSION AND SUMMARY

1. Auscultation of the heart is a subjective examination with definite limitations, which include its failure to provide a permanent record. 2. A new device for simultaneous, visual and audible recording of the heart acoustics is described. The record can be reproduced audibly for eventual study and comparison. 3. The permanent audible and visual record of the heart phenomena, the audio-visocardiogram, will reduce the margin of possible errors so often encountered in auscultation and may prove of value in a variety of medical fields.

REFERENCES

1. Rappaport, M. B., and Sprague, H. B.: Physiologic and Physical Laws that Govern Auscultation, and Their Clinical Application, Am. Heart J. **21**:257, 1941.
2. Rappaport, M. B., and Sprague, H. B.: The Graphic Registration of the Normal Heart Sounds, Am. Heart J. **23**:591, 1942.
3. Laënnec, R. T.: De l'ausculation mediate ou traité du diagnostic des maladies des poumons et du coeur fondé principalement sur ce nouveau moyen d'exploration, Paris, 1819, Brosson et Chaude.
4. Lian, C.: Le troisieme bruit du coueur, Semaine d. hôp. Paris **3**:596, 1927.
5. Braun, Menendez E., and Orias, O.: Estudio fonocardiografico en cien adultos jovenes, Rev. argent. de cardiol. **1**:101, 1934.
6. Calo, A.: Atlas de Phonocardiographie clinique, Paris, 1938, Masson et Cie.
7. Mannheimer, E.: Calibrated Phonocardiography. A New Technique for Clinical Use, Am. Heart J. **21**:151, 1941.
8. Orias, O., and Braun, Menendez E.: Heart Sounds in Normal and Pathological Conditions, London, 1939, Oxford University Press.
9. Trendelenburg, F.: Ueber physicalische Eingeschaften der Herztoene Naturwissenschaften Veröffentl **6**:184, 1927.
10. Levine, S.: Clinical Heart Disease, Philadelphia, 1937, W. B. Saunders Company.
11. Smith, J. R., Edward, J. G., and Kountz, W. B.: The Use of the Cathode Ray for Recording of the Heart Sounds and Vibrations, Am. Heart J. **21**:228, 1941.
12. Wells, B. G., Rappaport, M. B., and Sprague, H. B.: The graphic Registration of Basic Diagnostic Murmurs, Am. Heart J. **37**:584, 1949.
13. Lian, C., Minot, G., and Welti, J. J.: Phonocardiographie, Ausculation Collective, Paris, 1941, Masson & Cie.

THE HEART SCARAB OF THE ANCIENT EGYPTIANS

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". . . I will take the stony heart out of their flesh
And give them a heart of flesh."

Ezekiel XI, 19.

FOR more than a thousand years the ancient Egyptians, performing ritual autopsies on their dead, removed the viscera and replaced the heart with a stone carved in the form of a scarabaeus beetle. The ritual apparently had antecedents in the custom of stuffing the heart with linen cloth, possibly to maintain its shape.* Later the heart was removed along with the other viscera and its place was taken by the scarab amulet (Fig. 1). The earliest heart scarabs appeared during the second intermediate period (around 1700 B.C.)[1] and became common during the Empire period (1580 to 1150 B.C.). In other periods the scarab was placed on a necklace, or it was painted on the sarcophagus of the deceased. The custom waned along with the end of the practice of mummification and disappeared entirely by the time of the Christian conversion.

Numerous inquiries have been made into the significance of the replacement of the heart by the stone scarab. These have included the concept of substitution, that of the magical significance of the beetle in the act of resurrection, as well as etymological and literary convergences.

The concept of substitution was well engrained in the beliefs of the people. Thus substitute heads were sometimes placed in the tomb in order to assure that the deceased would be able to continue the important functions of this part (especially eating and speaking) even if the real head were lost. Substitutes for servants were supplied by statuettes whose duty it was to cater to the physical needs of their masters. Sethe[1] and Ward[2] have interpreted the heart scarab in this light, presuming the stone to act as a spare or "ersatz" heart in case of loss of the original.

The use of a scarab form for replacement of the heart contains many mystical elements which do not depend primarily on the proxy concept. The heart played a role in expressing the "Ka" or one of the spirits of man.[3] In this sense the heart was not so much an organ as a representation of the person or his spirit. It there-

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*This method of stuffing the heart with cloth is employed in modern pathologic techniques in order to maintain intracardiac relationships.

fore was a very necessary possession without which he could not be born again.[4] Ward suggests that the heart scarab had the magical power of restoring life to the deceased on the day of resurrection. Philologically, the Egyptian word for scarab, *kheper*, meant "becoming," "being," "metamorphosing." The association with the re-"becoming" of the deceased is apparent in this context.

As in the present day the heart was associated, at least in literary fashion, with such emotional qualities as sadness, fear, weakness, desire, courage, and love.[5] The heart was the "touch" or "feeling" of the viscera, giving life and health to the flesh.[6] The heart was also the center for conscience, memory, thought, and wisdom.[3,4] Its activity was synonymous with life.[6] Thus the Papyrus Ebers states that the heart speaks through the (pulse in the) extremities.[7,8]

Fig. 1.—A heart scarab. The obverse is inscribed with an incantation addressed to the heart. Discussed in text. Original in the Oriental Museum, University of Chicago.

The conjunction of heart and scarab probably arises from two sources. The commonly accepted explanation depends on the important role of the scarab in the ancient Egyptian religion, in which it was a common symbol. From the earliest times scarabs were used as seals to record official and historical events as well as for talismanic and funerary purposes.[9] The scarab (kheper) held a high place in the minds of these ancient people because they observed this insect in the act of rolling up balls of excrementous material and dust, in which the female deposited its eggs. Peculiarly, the Egyptians believed that all the beetles were

males and that the young beetles were generated spontaneously from the dust.[4,10-12] In this way the beetle (kheper) represented Khopri, the Father of the Gods, who created all things out of clay.[11] The beetle thus became the symbol and hieroglyph for generation, new life, virility, and resurrection.[4,5,10-12] The similarity between the rolling of the sun across the skies and the behavior of the scarab in rolling its ball of dung identified it with Ra, the sun god. The scarab thus brought the wearer the powerful protection of the gods. Pieper[13] felt that the Egyptians may have concluded that the heart was nothing other than a large, mystical scarab.[14]

Fig. 2.—A heart scarab showing a more obvious cardiac representation with auricles, but with no interventricular groove. The obverse is lined but for some reason was not inscribed. Original in the Oriental Museum, University of Chicago.

Inspection of some of the scarabs leads us to the suggestion that these were substituted for the heart by ancient embalmers who observed the superficial similarity between the dorsum of the stylized scarab and the surface appearance of the human heart (Fig. 1). The prothorax of the insect may have been identified with the auricles, the elytra (wing covers) seen as the ventricles, with the separation between the wing covers as the interventricular septum and coronary vessels. The head and limbs of the insect may have been compared to or identified with the large vessels entering and leaving the heart. The gradual change in stylistic approach with the occasional representation of the heart in a clearer fashion by the use of carvings with the *ib* (actual heart) representation (Fig. 2) may be considered to support this interpretation.

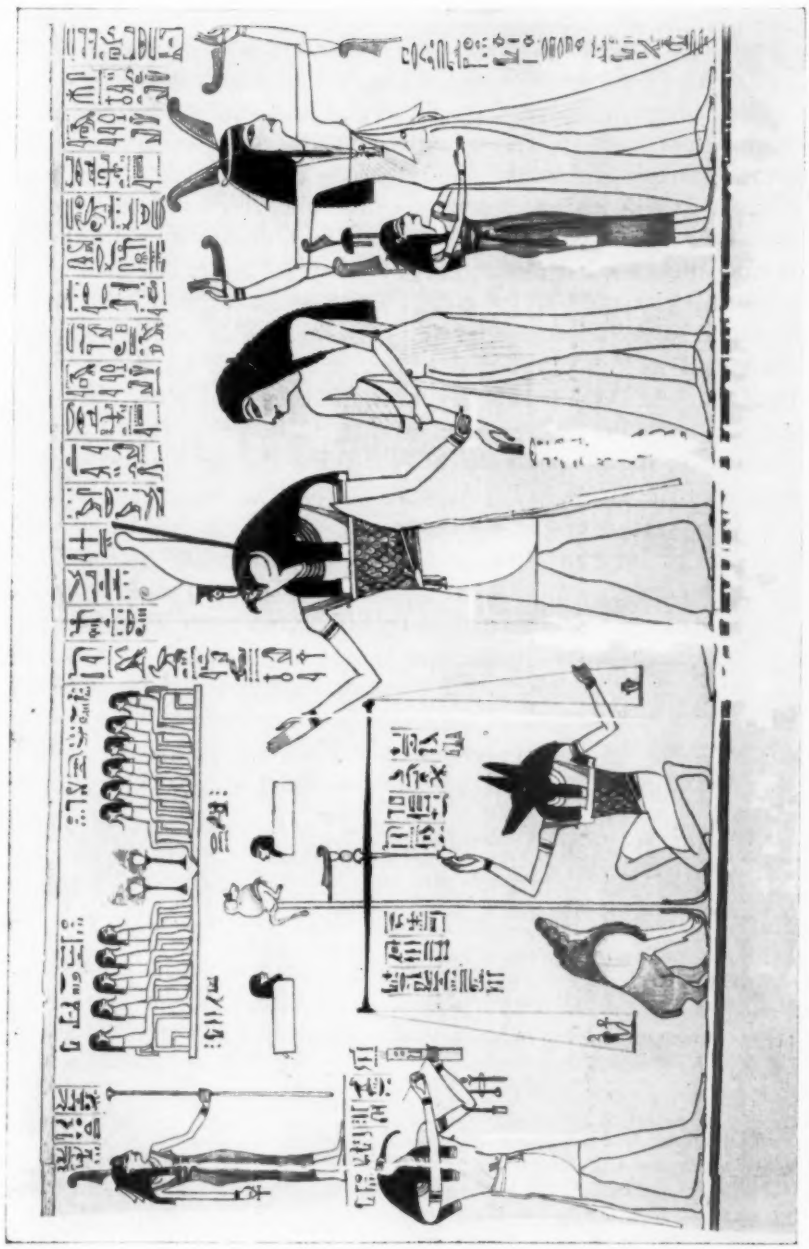

Fig. 3.—A vignette from the Book of the Dead illustrating the scene at the Weighing of the Heart. The deceased, Lady Anhai, is led to the scales by an attendant. The heart (ib) is weighed against the feather of truth, represented in this case by a figure of Ma'at with a feather headdress, while the monstrous Eater of the Dead looks on impatiently. The assessors sit impassively in the panel at the upper left. Ma'at herself oversees the scene from the commanding upper left. At the right, the deceased, vindicated and garlanded with feathers of purity, is led by a servant into the presence of Osiris. Discussed in text. From the Book of the Dead: Papyrus of Anhai, plate 4, British Museum.

The obverse of some of the early heart scarabs was inscribed with the name of its owner. More commonly they contained an inscription of a magic spell related to the role of the heart in the last judgment of the deceased (Fig. 1). The most common inscription was that of Chapter 30 b of the Book of the Dead.[15] In this book of prayers and incantations, a copy of which was often placed in the sarcophagus, a vignette shows the deceased in the Hall of Truth in the palace of Osiris (Fig. 3). The Judgment Tribunal consisted of Ma'at, the goddess of Truth, and 42 demigod assessors, each of whom had responsibility for specific kinds of sins. An important feature of this judgment scene is the weighing of the heart of the deceased against the feather of truth. At this time, the deceased gives the "Negative Confession," swearing that he has not lied, committed murder or adultery, stolen from the gods, been vain, haughty, or cruel and a large variety of other common defections from the moral code. The heart was then placed on the scale and weighed against the feather of truth. If the heart was weighed down by the sins of the deceased, and therefore heavier than truth, an attendant monster, the "Eater of the Dead" would seize and devour it and thereby destroy the opportunity of the defendant for life in the nether world. If, however, the heart were light and therefore pure, the deceased would be led into the glorious presence of Osiris, the great god of the dead.

Many of the incantations of the Book of the Dead are designed to protect the heart against loss or injury. Thus in Chapter 26, the vignette shows the deceased holding the hieroglyph of the heart (ib) against his breast while affirming, "My heart is mine, in the place of hearts." In Chapters 28 and 29 appropriate incantations and prayers meet the danger of loss of the heart to various and sundry demons. After surviving the extrinsic perils described in these and other chapters, the primary threat to resurrection appears to reside in the heart itself. On completing the "Negative Confession" in the Hall of Truth, the deceased addresses himself directly to his heart by commanding it not to bear evidence against him.

The chapter of the Book of the Dead with which the heart scarab is inscribed, refers to "Not letting the heart of the man act against him in the nether-world." The common text of the magic spell is—

> "My heart that I got from my mother,
> My heart necessary for my living on earth,
> Do not rise against me;
> Do not bear witness as an opponent to me among the circle of gods,
> On account of what I have done."

In other versions, the heart is adjured—

> "Stand not against me as a witness;
> Create not opposition against me among the assessors;
> Do not weigh heavy against me
> In the presence of the Keeper of the Scales." (6, 9, 12, 15)

Since the Egyptians viewed the heart as having qualities of separate entity (ka), Chapter 30 would appear to be designed primarily to gain control of the heart and thus prevent it from betraying its owner at the critical time of the judg-

ment. This anxiety suggests to us that the ancients were fully cognizant of the potential autonomous behavior of the heart, independent of the will of its owner. The heart was recognized as a threatening conscience which might not be adequately controlled without appropriate magic. The incantation carved on the scarab served magically to gain control over the actions of the heart at such a critical time, and prevent it from acting as a lie detector so that the real moral stamp of its owner might not be revealed to the gods.*

From the point of view of the research discipline, it may be considered rather disappointing that the ancient Egyptians, performing untold thousands of autopsies on their dead, had so little useful information concerning the function of the myocardium in normal and diseased states. Undoubtedly very large segments of the art of medicine of those times have been lost. A certain amount of rational information concerning surgical techniques was available, as indicated in the Edwin Smith papyrus. However, it appears that useful knowledge of internal diseases was extraordinarily limited. Some of the Egyptian medicine was transmitted to the Greeks, but even so there is little evidence of progress commensurate with such a long and rich experience.[18-20]

Untold numbers of examinations on the bodies of subjects with the whole spectrum of diseases of the heart and the other viscera were made by intelligent men for a period of three thousand years. Presumably one of the primary reasons for the failure to gain useful information from these ritualistic examinations was due to the paucity of adequate theory to guide their observations. Only the development of adequate theory and practice of the scientific method could gain the victory of free inquiry over dogma and open the way for progress.

SUMMARY

Previous suggestions concerning the meaning of the scarab are reviewed. It is suggested that the convergence of the heart and the scarab concepts arose from the superficial similarities in form between the dorsum of the scarab and the ventral appearance of the human heart.

The role of the heart in the judgment scene is depicted in relation to the inscription on the reverse of the heart scarab. This incantation is interpreted as a device to prevent the heart from behaving as a lie detector at the crucial moment of the last judgment.

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*This irreverent theme appears in the *Solemn Festal Dirge of the Ancient Egyptians* (*Egyptian Literature*, C. W. Goodwin, New York, 1901, Colonial Press) which was sung at the entertainments of the wealthy. After reminding the celebrants of the inevitability of death, the guests are advised:

". . . Strengthen thine heart to forget
How thou hast enjoyed thyself.
Fulfill thy desire while thou livest . . .
Lamentations deliver not him who lies in the tomb;
Feast in tranquility
Seeing that none carries his goods away with him."

I wish to acknowledge the generous advice and suggestions of Dr. K. C. Seele, of the Oriental Institute of the University of Chicago.

The figures are from material in the collection of the Oriental Institute, University of Chicago.

REFERENCES

1. Sethe, K. H.: Zur Vorgeschichte der Herzskarabäen, Mem. publ. p. l. Membres l'Inst. Franc. d. Arch. Orientale du Caire **66**:113, 1935-1938.
2. Ward, J.: The Sacred Beetle, London, 1902, John Murray.
3. Spiegelberg, W.: Das Herz als Zweites Wesen des Menschen, Ztschr. f. Ägypt. Sprache und Altertumskunde **66**:35, 1930.
4. A General Introductory Guide to the Egyptian Collections in the British Museum, London, 1930, p. 217, British Museum.
5. Piankoff, A.: Le coeur dans les textes Egyptiens depuis l'ancien régime jusqu'à la fin du Nouvel Empire, Paris, 1930, Libraire Orientaliste Paul Guenther.
6. Birch, S.: On Formulas Relating to the Heart, Ztschr. f. Agyp. Sprache u. Altertums kunde **8**:73, 1867.
7. The Papyrus Ebers, Translated by B. Ebbell, London, 1937, Milford, Oxford U.
8. Hamburger, W. W.: The Earliest Known Reference to the Heart and Circulation, Am. Heart J. **17**:259, 1939.
9. Knight, A. E.: Amentet: An Account of the Gods, Amulets and Scarabs of the Ancient Egyptians, London, 1915, Longmans Green & Co.
10. Birch, S.: On Formulas Relating to the Heart, Ztschr. f. Ägypt. Sprache und Alterstumkunde **5**:54, 1867.
11. Newberry, P. E.: Egyptian Antiquities: Scarabs, London, 1906, Constable & Co., Ltd.
12. Engelbach, R.: Introduction to Egyptian Archaeology, Inst. Franc. de Arch. Orientale, 1946.
13. Pieper, *Quoted* in Reference 14.
14. Wessetzky, W.: Jubilee Volume in Honor of Edward Mahler on his 80th Birthday, Budapest, 1937.
15. Davis, Charles H. S.: The Egyptian Book of the Dead, New York, 1895, Knickerbocker Press.
16. Budge, E. A. W.: The Mummy: A Handbook of Egyptian Funerary Archeology, Cambridge, 1925.
17. Rowe, A.: A Catalogue of Egyptian Scarabs in the Palestine Arch. Museum, Inst. Franc. d'Arch. Orientale, 1936.
18. Ranke, H.: Medicine and Surgery in Ancient Egypt, Bull. Inst. Hist. Med. **1**:237, 1933; in Bull. Johns Hopkins Hosp., Aug. 1933.
19. Krause, A. C.: Ancient Egyptian Ophthalmology, Bull. Inst. Hist. Med. **1**:258, 1933; in Bull. Johns Hopkins Hosp., Aug. 1933.
20. Sigerist, H.: A History of Medicine. Volume I. Primitive and Archaic Medicine, New York, 1951, Oxford University Press.

Clinical Reports

CONGENITAL AORTIC ATRESIA AND HYPOPLASIA OF THE AORTIC ORIFICE

Case Reports on Two Members of a Family

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PRIMARY malformation of the aortic orifice, either complete atresia or marked hypoplasia, is a rare cardiac anomaly. In either case, there is defective development of the aorta proximal to the entrance of the ductus arteriosus and hypoplasia of the left ventricle and mitral valve. As a result of the abnormal circulation, the ductus arteriosus and foramen ovale are patent and the right atrium, right ventricle, and pulmonary artery are enlarged. The malformation is usually compatible with life for only a few days.

In Abbott's atlas of congenital heart disease,[1] twelve cases of aortic atresia are recorded. Gunn and Miale[2] located four additional cases of this nature and reported one of their own. Dry and associates[3] in a clinicopathologic study of 132 cases of congenital anomalies of the heart and great vessels reviewed seven cases of aortic atresia. Friedman and associates[4] reported six cases of aortic atresia with hypoplasia of the left side of the heart and aortic arch. In a careful search of the literature, they found only thirty-two other cases in which the primary malformation was atresia of the aortic orifice, making a total of thirty-eight reported cases. Cases with associated deformity or atresia of the mitral valve were excluded from their series.

Only a few cases of congenital heart disease in members of the same family have been reported. The following cases are reported because of the unusual occurrence of a rare cardiac malformation in two members of a family.

CASE REPORTS

Case 1.—The mother was 20 years old and in good health. She had had one previous pregnancy with spontaneous delivery of a full term stillborn infant. An autopsy was not performed. The mother was Rh negative. The Kahn test was negative.

The second pregnancy was uneventful and on March 22, 1949, a full term boy infant was delivered spontaneously. The birth weight was 8 pound 2 ounces. The infant was cyanotic and dyspneic at birth and was immediately given oxygen. This reduced the cyanosis to some extent.

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The lungs were clear. The heart sounds were good and no murmurs were heard. The liver was enlarged. Roentgenologic studies of the chest revealed considerable widening of the cardiac and mediastinal shadows. The cyanosis and dyspnea increased in spite of oxygen. The baby expired March 24, approximately thirty-seven hours after birth.

Post-mortem examination revealed a well nourished, white boy, weighing 3,650 grams. There was cyanotic discoloration of the face, neck, and extremities. There were no external malformations.

There was no fluid in the pleural cavities. The right lung weighed 35 grams. The left lung weighed 38 grams. Crepitation was diminished in all lobes and abundant bloody fluid exuded from the cut surfaces.

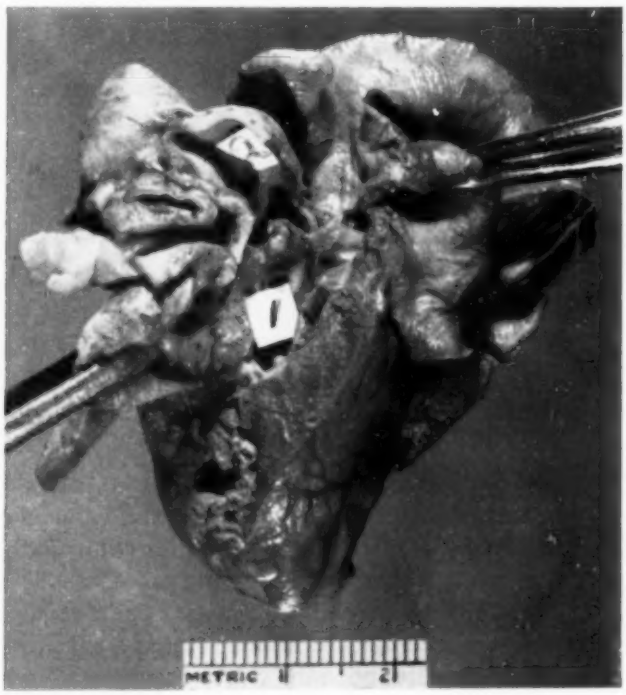

Fig. 1.—Case 1, the heart is opened to show the hypoplastic left ventricle *1*, aortic orifice and ascending aorta *2*.

The thymus was normal in size and appearance. The pericardial sac was normal in appearance and contained no excess fluid.

The heart, which weighed 26 grams, showed marked enlargement of the right atrium and right ventricle. Opening the heart revealed wide patency of the foramen ovale. The tricuspid valve was dilated; it measured 40 mm. in circumference. The right ventricle was markedly dilated and hypertrophied. The pulmonary artery, which arose from the right ventricle, was also dilated. The ductus arteriosus was widely patent and of the same caliber as the pulmonary trunk and descending aorta. The pulmonary artery divided normally into its right and left branches and continued as the ductus arteriosus into the descending aorta giving the appearance of one continuous vessel. The left atrium was small but well formed. The mitral valve was reduced in size but normal in appearance. It led into a hypoplastic left ventricle whose cavity measured 7 mm. by 4 mm. The interventricular septum was intact. The cusps of the aortic valve were fused forming a small orifice 2 mm. in diameter. The coronary arteries arose normally. The aorta, which gave off its three main branches at the arch, remained narrow until it reached the point of entrance of the ductus arteriosus.

The liver weighed 150 grams and a large amount of blood escaped from the cut surface. The other organs showed no gross abnormalities.

Microscopic examination of sections from the myocardium and endocardium did not show any evidence of inflammation or scarring.

The anatomic diagnosis was hypoplasia of the aortic orifice; hypoplasia of the left atrium, mitral valve, left ventricle and ascending aorta; patency of the foramen ovale and ductus arteriosus; hypertrophy of the right atrium, right ventricle, and pulmonary artery.

CASE 2.—On Feb. 5, 1951, the same mother gave birth to another full term male infant weighing 6 pounds, 13 ounces. The infant was cyanotic at birth and was given oxygen continuously. The cyanosis decreased for a while. The next day the respirations were labored and the cyanosis was marked. The lungs were clear. No murmurs were heard. The liver was enlarged.

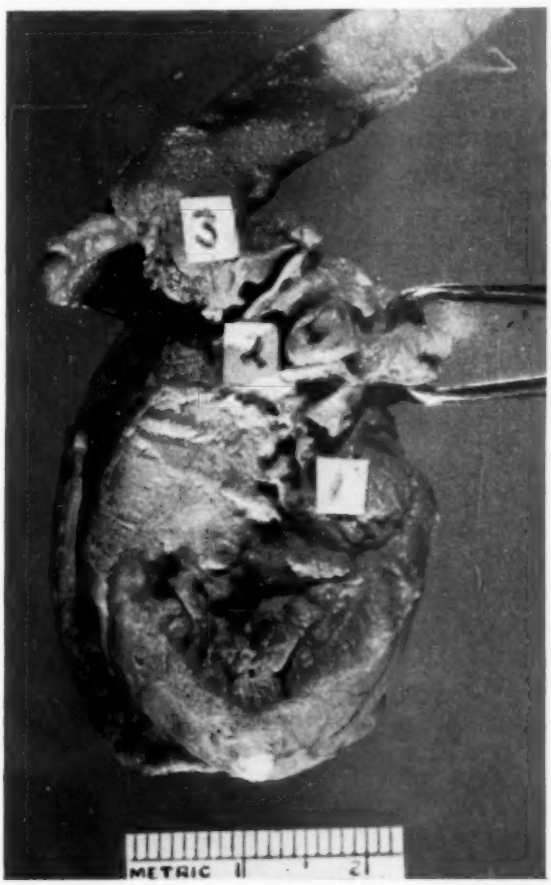

Fig. 2.—CASE 2, the heart is opened to show the rudimentary left ventricle *1*, atretic aortic orifice *2* and widely patent ductus arteriosus *3*.

Roentgenologic studies of the chest revealed the heart to be somewhat globular in shape. There was slight prominence of the upper mediastinum. The lung fields were clear.

The cyanosis and dyspnea increased in spite of oxygen. The infant expired on Feb. 7, 1951, approximately fifty-three hours after birth.

Post-mortem examination revealed a well nourished, white boy measuring 50 cm. in length. There was cyanotic discoloration of the face, neck, and extremities, but no external malformations

Each pleural cavity contained about 25 c.c. of clear straw-colored fluid. Each lung weighed 30 grams. Crepitation was diminished in all lobes and a moderate amount of blood exuded from the cut surfaces.

The thymus was normal in size and appearance. The pericardial sac was normal in appearance and contained no excess fluid.

The heart, which weighed 26 grams, showed marked dilatation and hypertrophy of the right atrium and right ventricle. The foramen ovale was widely patent. The tricuspid valve was dilated. It measured 42 mm. in circumference. There were no defects in the interventricular septum. The pulmonary artery, which stemmed from the right ventricle, divided into its right and left pulmonary branches and then continued as the ductus arteriosus into the descending aorta. The ductus arteriosus was widely patent and of the same caliber as the dilated pulmonary trunk and descending aorta giving the impression of one continuous vessel. The left atrium was small but well formed. The mitral valve was a very small structure with two dimunitive cusps attached to fine papillary muscles. Its minute orifice led into a rudimentary left ventricle. The cavity of the left ventricle, which was imbedded in the wall of the hypertrophied right ventricle, measured 3 mm. by 2 mm. There was complete atresia of the aortic valve, and a fine probe could not be passed from either the ventricular or aortic side. The ascending aorta was a narrow tube ending blindly in the muscle at the base of the left ventricle. The coronary arteries arose normally. The aorta, from which the great vessels arose in normal fashion, remained narrow until the point of entrance of the abnormally wide ductus arteriosus.

The peritoneal cavity contained about 100 c.c. of clear straw-colored fluid. The liver weighed 130 grams and a large amount of blood escaped from the cut surface.

Microscopic sections of the myocardium and endocardium did not show any evidence of inflammation or scarring.

The anatomic diagnosis was complete atresia of the aortic orifice; hypoplasia of left atrium, mitral valve, left ventricle, and ascending aorta; patency of the foramen ovale and ductus arteriosus; hypertrophy of the right atrium, right ventricle, and pulmonary artery.

COMMENT

In these cases the primary malformation is defective development of the aortic orifice. The first infant had hypoplasia of the aortic orifice, and the second infant had complete atresia of the aortic orifice. As a result of atresia or marked hypoplasia of the aortic orifice, there is underdevelopment of the left ventricle and ascending aorta. Atresia of the aortic orifice prevents the expulsion of blood from the left ventricle into the ascending aorta. Atresia or hypoplasia of the left ventricle affects the expulsion of blood from the left atrium. Consequently, the blood entering the left atrium from the lungs passes through the foramen ovale into the right atrium and then into the right ventricle. The blood from the systemic circulation is returned in normal fashion to the right ventricle. The mixture of venous and oxygenated blood is pumped by the right ventricle into the pulmonary artery. Some blood enters the right and left pulmonary branches to reach the lungs, and the rest flows through the ductus arteriosus into the aorta. Retrograde flow from the ductus arteriosus to the base of the aorta supplies the coronary vessels and the great vessels of the aortic arch. The right ventricle, which pumps blood not only to the lungs but to the systemic circulation, hypertrophies from excessive work. Patency of the foramen ovale and of the ductus arteriosus is necessary to maintain the abnormal circulation (See Fig. 3).

The mode of origin of these defects is speculative. Some observers believe that the genesis is inflammatory and interpret the finding of myocardial scarring and cellular infiltration as evidence of healed fetal endocarditis or myocarditis.

Since the valvular stenosis is not associated with septal defects, it has been suggested that the intracardial infection occurred after the heart was completely formed but still small. However, it does not seem probable that an inflammatory process could produce this type of anomaly so uniformly. In the cases presented above, there was no evidence of scarring or inflammation.

Some observers believe that the malformation results from errors in the development of a four-chambered heart from the primitive cardiac tube. The development of the embryo is affected by both extrinsic and intrinsic factors. It is recognized that German measles in the first trimester of pregnancy is associated with a high incidence of congenital anomalies. Friedman and associates[4] state that it is probably correct to consider infection as one of the many agents capable of inciting developmental errors.

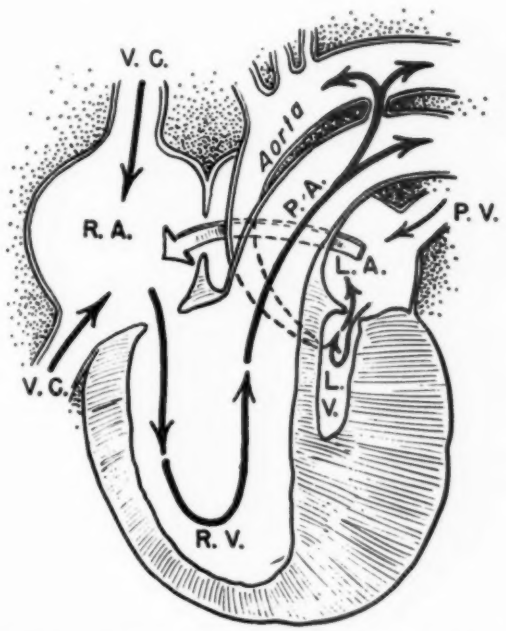

Fig. 3.—Diagram of intracardiac circulation in aortic atresia. (Courtesy Dr. T. J. Dry and Postgraduate Medicine. From Postgrad. Med., vol. 4, 1948).

Heredity may be a factor in the production of cardiac malformations. Walker and Ellis[5] reported two families and found forty-eight other families recorded in the literature in which there were multiple instances of congenital malformations of the heart, fifteen in more than one generation. Taussig[6] states that she has seen four families in whose members there were multiple instances of congenital malformation of the heart, in two of these families in more than one generation. Stein and Barker[7] reported congenital heart disease in a mother and two children. The cases were coarctation of the aorta in the mother and patency of the ductus arteriosus in the son and daughter. An interesting summary of the early literature on the subject of familial congenital heart disease is given by Snelling.[8]

As stated by Walker and Ellis,[5] ". . . since most patients with congenital heart disease die young, or if they live to maturity, are likely to be sickly and not bear children, any inheritance of this condition is seldom carried directly. Indeed the remarkable thing is, not that so few cases of inherited congenital heart disease have occurred, but that there has been so much inheritance of a condition so ill adapted to biologic self-perpetuation." According to Taussig[6] the current belief is that if a malformation occurs in one offspring, there is a 20 per cent chance that there will be some abnormality in the subsequent offspring of the same mating and a 2 per cent chance of the recurrence of the identical malformation.

SUMMARY

A case of atresia of the aortic orifice and a case of hypoplasia of the aortic orifice occurring in members of the same family are reported. Both were associated with hypoplasia of the left ventricle and ascending aorta, patency of the foramen ovale and of the ductus arteriosus, hypertrophy of the right ventricle and right atrium.

REFERENCES

1. Abbott, M.: Atlas of Congenital Carciac Disease, New York, 1936, American Heart Association, p. 48.
2. Gunn, James A., and Miale, J. B.: Aortic Atresia, Mitral Stenosis, Hypoplasia of the Left Ventricle and Other Cardiac Anomalies in Newborn, Arch. Path. **50**:464, 1950.
3. Dry, T. J., Edwards, J. E., Parker, R. L., Burchell, H. B., Rogers, H. M., and Bulbulian, A. H.: Congenital Anomalies of the Heart and Great Vessels, Postgrad. Med. **4**:327, 1948.
4. Friedman, S., Murphy, L., and Ash, R.: Aortic Atresia With Hypoplasia of The Left Heart and Aortic Arch, J. Pediat. **38**:354, 1951.
5. Walker, G. C., and Ellis, L. B.: The Familial Occurrence of Congenital Cardiac Anomalies, Proceedings, New England Heart Association, 1940-41, pp. 26-27.
6. Taussig, Helen B.: Congenital Malformations of the Heart, New York, 1947, The Commonwealth Fund, p. 8.
7. Stein, Isidore, and Barker, Donn. J.: Congenital Heart Disease. Case Reports on Three Members of a Family, Am. Heart J. **30**:118, 1945.
8. Snelling, David B.: Familial Congenital Heart Disease, J. A. M. A. **108**:1052, 1937.

FATAL REACTION TO 1-HYDRAZINOPHTHALAZINE (APRESOLINE)

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FOUR YEARS of clinical experience with the compound 1-hydrazinophthalazine (Apresoline) have demonstrated it to be a moderately potent antihypertensive drug. Recent reviews[1-6] deal exhaustively with the experimental background and clinical pharmacology of this compound, and the interested reader is referred to their extensive bibliography. These studies indicate that 1-hydrazinophthalazine induces its hypotensive effects through a variety of sites and modes of action. Renal and peripheral blood flows are increased[7,8] and an additional locus of action in the mid and hindbrain has also been postulated.[8,9] Humoral pressor agents including hypertension,[2,3] pherentasin,[2,3] sustained pressor principle,[2,3] serotonin,[10] nor-epinephrine,[11] and a cerebral vasopressor substance[10,12] are antagonized in varying degree. Clinically, 1-hydrazinophthalazine has proved useful in the treatment of sympathectomy failures,[2] in "benign" hypertension,[3,6] and in a variable proportion of cases of "malignant" hypertension.[2,3,5] Observations[14] have indicated that this compound may be a valuable agent in the management of patients with late toxemias of pregnancy and other types of hypertensive disease associated with the gravid state. It appears to act synergistically when employed in combination with hexamethonium and veratrum viride[3,5,6,13] and its effects may be potentiated by salt restriction.[2,5] No enhancement of effect has followed the combination of 1-hydrazinophthalazine with Priscoline or Regitine.[2]

Although side effects are not infrequent with the use of 1-hydrazinophthalazine, fatalities have been uncommon. This is a report of fatal outcome following oral administration of this drug in a patient with pre-eclamptic toxemia.

CASE REPORT

R.N., a Pima Indian, was first seen in the Outpatient Department of the Phoenix Medical Center Hospital at the age of 25, at which time she was discovered to be in the initial trimester of her first pregnancy. She was otherwise asymptomatic. Blood pressure was 110/60 mm. Hg and physical examination was unremarkable except for the gravid state. Repeated prenatal examinations including blood pressure and urinalysis on each visit were within normal limits. She was delivered at term of a living girl and her post-partum course was without incident. Examination fifteen months later prior to employment disclosed no abnormalities.

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One year later (three years after her initial visit) she was again seen in the Outpatient Department of the Phoenix Medical Center Hospital, and was found to be approximately seven months' pregnant. Blood pressure was 135/80 mm. Hg and there were no abnormalities on physical examination. Serologic tests for syphilis were negative. Urinalysis indicated a specific gravity of 1.024 and negative tests for protein and sugar; only occasional crystals were seen in the microscopic examination of the centrifuged sediment. Hemogram was within normal limits. She was asymptomatic on the next prenatal visit, three weeks later. The blood pressure was 150/100 mm. Hg, eyegrounds were clear, the heart was unenlarged, and there was no evidence of limited cardiac reserve. Urinary specific gravity was 1.032, there was 1-plus proteinuria and occasional white blood cells were noted in the centrifuged sediment. Blood nonprotein nitrogen was 42 mg. per cent (normal 35 to 45 mg. per cent. A low salt (4 Gm. daily) diet was prescribed.

One week later the patient was seen in the Outpatient Department, complaining of vertigo without syncope, and a severe throbbing frontal headache. The blood pressure was 165/110 mm. Hg, but no retinal or cardiovascular abnormalities were noted. Urinary specific gravity was 1.022, with 1 plus proteinuria without pyuria or cylindruria. In view of her sustained hypertension and marked symptomatic complaints it was decided to begin treatment with 1-hydrazinophthalazine (Apresoline). Hospitalization was advised but was declined by the patient who preferred to be seen daily in the Outpatient Department. The following day 1-hydrazinophthalazine was begun in a dose of a single 25 mg. tablet after each of the three meals. Three hours following the third dose of the drug she was awakened from a nap by a severe constricting left chest pain which was nonradiating and accompanied by a cold perspiration and a sense of imminent dissolution. Because of persistence of the pain over the next hour she came to the Receiving Room of the Phoenix Medical Center Hospital.

Examination disclosed an acutely ill young woman with an ashen countenance. Blood pressure was 100/60 mm. Hg, pulse 76 and respirations 22 per minute. There were occasional ventricular extrasystoles but no evidence of cardiac decompensation. The fetal heart rate was 140 and regular in rhythm. An electrocardiogram showed a P-R interval of 0.14 second and a corrected Q-T interval of 0.40 second; the QRS complex measured 0.08 second. There was moderate clockwise rotation of the heart in the semivertical position. T_3 was inverted and T waves in the unipolar precordial leads were uniformly low. It was thought that this represented an episode of hypotension with coronary insufficiency secondary to the use of 1-hydrazinophthalazine. Hospitalization was again advised but was declined by the patient who left for home after her precordial pain had been relieved by a hypodermic injection of 100 mg. Demerol Hydrochloride. She was advised to discontinue the use of 1-hydrazinophthalazine.

Twelve hours later the patient was seen at home by a private physician. At this time she was asymptomatic save for a mild headache, and stated that she had slept comfortably after the previous night's hypodermic medication. Blood pressure was 160/120 mm. Hg and she was otherwise normal. 1-hydrazinophthalazine was prescribed without knowledge of its previous use, and the patient again took a 25 mg. dose orally after breakfast, lunch and supper. Two hours following the third dose of the drug she complained of drowsiness and gradually lapsed into coma; she was brought to the Phoenix Medical Center Hospital and admitted.

On admission she was comatose, pale, and was covered with cold perspiration. Blood pressure was 110/50 mm. Hg, pulse rate was 56; there was a basically regular rhythm with frequent ventricular extrasystoles. The lungs were clear. Fetal heart rate was 88 and its rhythm regular. There was no peripheral edema. She responded poorly to painful stimulation. There was anisocoria with a dilated fixed left pupil; fundi were normal. Abdominal reflexes were absent, and there were no deep tendon reflexes. Babinski and Hoffmann signs were present bilaterally. There was no evidence of meningeal irritation. Modalities of sensation could not be evaluated. Laboratory examination indicated a normal hemogram. A catheterized urine specimen totalled only 50 c.c. of brownish, turbid, fluid of specific gravity 1.026 with 4 plus proteinuria. Numerous finely granular, hyaline and waxy casts, as well as a few red and white blood cells were seen in the urinary sediment on microscopic examination.

Supportive therapy was begun with intravenous alimentation and parenteral antibiotics. One hour after entry the blood pressure rose to 190/120 mm. Hg, and was sustained at levels of

160 to 190 mm. Hg systolic and 120 to 135 mm. Hg diastolic during the remainder of the hospitalization. There was total suppression of urinary output during this period. One and one-half hours following entry the patient had the first of several generalized convulsions. The fetal heart beat was imperceptible. Respirations became increasingly rapid and pulmonary edema ensued which did not respond to conventional measures. The patient expired four and one-half hours after admission without having regained consciousness. Fetal death had occurred in utero.

Permission was granted only for *post-mortem* removal of tissue from the liver and kidneys for histologic examination. Histopathologic examination* of the . . . "liver shows two distinct types of lesions. The first type consists of scattered patches of liver cells containing large cytoplasmic vacuoles with the nuclei pushed to the side of the cell. There is no relationship to lobular architecture and no necrosis of cells. Special stains show that the cytoplasmic vacuoles contain fat. The second type of lesion consists of patchy groups of dilated spaces which are partially confluent and appear to compress the surrounding liver cells. They are most numerous in the subcapsular regions but are found throughout, and several such areas are in close relationship to portal areas. These spaces are filled with a fine cobweblike network which is similar to that found in a few of the blood vessels. No intact red blood cells are seen anywhere in the section, having apparently been destroyed in the fixation process. The larger lesions have fibrin thrombi in the center with local disruption of the liver architecture and moderate leukocytic infiltration. Special stains show little or no stainable fat in most of these lesions. The kidney tubules are dilated and may contain an acidophilic granular material. Some of the collecting tubules contain a similar granular material. The glomerular capillaries stand out prominently, but are empty of blood. The blood vessels appear normal and there is no stainable fat in the epithelium of the tubules.

"Diagnosis: Telangiectasia and partial necrosis, portal area, consistent with eclampsia. Kidneys—no pathologic diagnosis."

COMMENT

Although extensive laboratory evaluation was precluded by the brief period of hospitalization prior to death, and adequate post-mortem examination was not permitted, the close temporal relationship between the administration of 1-hydrazinophthalazine and subsequent untoward reaction on two occasions was striking. Hypotension and coronary insufficiency followed a total of 75 mg. of the drug given orally in divided doses over a twelve hour period, and subsided upon withdrawal of the medication. Hypotension and coma followed an identical dose inadvertently prescribed the next day by a physician who was unaware of the previous therapy. Death ensued during a second period of drug withdrawal which was characterized by hypertension, convulsions, and anuria with terminal pulmonary edema and fetal death in utero. That these effects were due to 1-hydrazinophthalazine seems inescapable.

Side effects of mild to moderate degree have been relatively frequent with the use of this antihypertensive agent alone or in combination with other drugs, and have been carefully tabulated by the manufacturer and interested groups of investigators. Postural hypotension, tachycardia, palpitation, dizziness, weakness, mild to severe headache, nausea and vomiting are, ". . . the side effects most frequently encountered."[4] Headache has been attributed to the release of histamine,[2,3] as well as to the sudden drop in arterial pressure; flushing, varying degrees of nasal congestion, lacrimation and conjunctival inflammation are not uncommon.[2-4,6] Antihistaminic agents may be useful in controlling these latter

*Rendered by the Pathology Laboratory, Experimental Biology and Medicine Institute, National Institutes of Health, Bethesda, 14, Md.

manifestations.[2-4] Edema and mild anemia,[15] high fever,[16] skin rash and urticaria,[6] as well as bladder disturbances[5,16,17] have been noted. An excessive desire to defecate may be induced in patients previously subjected to sympathectomy.[2] These untoward side effects have been considered troublesome rather than dangerous, and may disappear with continued treatment.[2,4] Cumulative toxicity is considered infrequent.[3,4]

Unfortunately, more profound misadventures have marked the use of 1-hydrazinophthalazine in a number of instances. Schroeder, drawing on one of the most extensive experiences with the use of this compound, has wisely directed attention to the theoretical complications of normotension in cerebral, coronary, and renal areas which are involved in arteriosclerotic changes.[3] Uremia, cerebral vascular accidents, angina pectoris, and multiple myocardial infarctions have followed too rapid reduction in blood pressure, particularly in cases of malignant hypertension.[3,16] Schroeder records[3] the onset of renal insufficiency in a 28-year-old Negro woman subsequent to hypotension induced by 1-hydrazinophthalazine in combination with hexamethonium; anuria accompanied the hypotensive state, and later escape of the blood pressure to previous high levels precipitated fatal pulmonary edema. Two fatalities in the experience of other physicians which were reported to Schroeder are listed in a footnote to his article. These three case reports resemble our own experience, reported herein, quite closely.

Sudden cessation of antihypertensive drug therapy may likewise be dangerous in the "malignant" stages, with death occurring within a very few weeks from a variety of cardiovascular, renal, and cerebral catastrophies.[16]

Grimson and associates[5] have summarized the extensive literature relating to the use of 1-hydrazinophthalazine and hexamethonium; they conclude that although hexamethonium is the more potent of the two, the use of either is not without potential danger. Statements or cautions are formulated in this important review which should be consulted by all those concerned with the treatment of hypertension with these drugs. It is their belief that therapy is best initiated during careful hospital observation, and the course of events in the case reported herein is tragic witness to the validity of this statement. Careful anamnesis, physical and laboratory evaluation are essential. Small doses should be employed cautiously in patients with encephalopathy, damaged myocardium, and diminished renal function, and in those with autonomic dysfunction, particularly patients previously treated by sympathectomy. The possibility of potentiation by sedatives, alcoholic beverages, and sodium-depletion diets should be taken into account. All patients should be schooled concerning the hazards and possible toxicity of these compounds, and the need for alteration of dosage according to symptomatology, if they are continued on an outpatient basis, should be made clear. Lastly, Grimson emphasizes the unpredictability of these drugs, and underscores the fact that their present use is largely on an experimental basis.

SUMMARY

A 28-year-old Indian woman suffering from pre-eclamptic toxemia developed severe precordial pain following too-rapid lowering of the arterial blood pressure

by 1-hydrazinophthalazine (Apresoline). Symptomatology regressed and the blood pressure returned to previously elevated levels following drug withdrawal. The medication was inadvertently resumed the next day and an identical oral dose was accompanied by hypotension, coma, and oliguria, succeeded by hypertension, convulsions, and fatal pulmonary edema with fetal death in utero. It is considered that this fatality was related to the use of 1-hydrazinophthalazine. The literature dealing with the clinical toxicity of this compound is reviewed briefly.

Correspondence with the manufacturer has confirmed the rarity of the reaction described above in the management of young patients without obvious compromise of coronary or cerebral vascular beds. It is felt that the fatality described may represent an episode of ultrasensitivity to 1-hydrazinophthalazine, and it is the manufacturer's recommendation that ambulatory therapy be instituted with the smaller 10 mg. tablets recently made available subsequent to our own experience.

REFERENCES

1. Page, I. H.: Treatment of Essential and Malignant Hypertension, J. A. M. A. **147**:1311, 1951
2. Schroeder, H. A.: The Effect of 1-Hydrazinophthalazine in Hypertension, Circulation **5**:28, 1952.
3. Schroeder, H. A.: Control of Hypertension by Hexamethonium and 1-Hydrazinophthalazine, Arch. Int. Med. **89**:523, 1952.
4. Apresoline: A New Antihypertensive Agent, Present Evaluation of Laboratory and Clinical Findings, Ciba Pharmaceutical Products, April 1, 1952, pp. 1-34.
5. Grimson, K. S., Orgain, E. S., Rowe, C. R., Jr., and Sieber, H. A.: Caution With Regard to Use of Hexamethonium and "Apresoline," J. A. M. A. **149**:215, 1952.
6. Johnson, R. L., Freis, E. D., and Schnaper, H. W.: Clinical Evaluation of 1-Hydrazinophthalzine (C-5968) in Hypertension, Circulation **5**:833, 1952.
7. Reubi, F. C.: Renal Hyperemia Induced in Man by a New Phthalazine Derivative, Proc. Soc. Exper. Biol. & Med. **73**:102, 1950.
8. Gross, F., Druey, J., and Meier, R.: A New Group of Depressor Substances With a Special Type of Effect, Experientia **6**:19, 1950.
9. Craver, B. W., and Yonkman, F. F.: Some Pharmacological Properties of 1-Hydrazinophthalazine, a Hypotensive Agent, Federation Proc. **9**:323, 1950.
10. Taylor, R. D., Page, I. H., and Corcoron, A. C.: A Hormonal Neurogenic Vasopressor Mechanism, Arch. Int. Med. **88**:1, 1951.
11. Freis, E. D., and Finnerty, F. A., Jr.: Suppression of Vasomotor Reflexes in Man Following 1-Hydrazinophthalazine (C-5968), Proc. Soc. Exper. Biol. & Med. **75**:23, 1950.
12. Editorial: Hormonal Cerebral Vasopressor Substance, J. A. M. A. **146**:1326, 1951.
13. Freis, E. D., Finnerty, F. A., Schnaper, H. W., and Johnson, R. L.: The Treatment of Hypertension With Hexamethonium, Circulation **5**:20, 1952.
14. Assali, N. S.: Unpublished Data *Quoted* in Hypertenso-vascular Progress, Ciba Pharmaceutical Products **1**:17, 1952.
15. Page, I. H.: *Quoted* in Grimson, K. S., et al., reference No. 5.
16. Schroeder, H. A., ibid.
17. Goldstein, M. R., Schloss, W. A., and Cohn, S. H.: Medical Intelligence: Bladder Disturbance Due to Apresoline, New England J. Med. **247**:525, 1952.

Book Review

RHEUMATISCHE ERKRANKUNGEN. Edited by Prof. Dr. Max Hochrein, Ludwigshafen. Stuttgart, 1952, Georg Thieme, Verlag, 340 pages, Price, DM 36.-

Under the heading "Rheumatic Diseases," this symposium covers a wide variety of conditions in which pain in some part of the locomotor system is an important manifestation. Thus, diseases affecting the bones, joints, muscles, the central and peripheral nervous systems, and certain disorders of metabolism are included.

The twenty-two contributors have presented a concise and comprehensive review of the various conditions in their respective specialties. The first part of the book deals mainly with pathogenesis, clinical manifestations, and differential diagnosis, while later chapters are devoted to discussions of various types of therapy and the relationship of focal and systemic infections, climate, and occupation on "rheumatic" manifestations.

The book is well illustrated with roentgenograms, diagrams, and charts. An extensive bibliography is provided containing mainly references to the recent European literature, and also to important publications from Britain and the United States.

The book is of value to students and general practitioners as an up-to-date review and a source of reference.

C.F.

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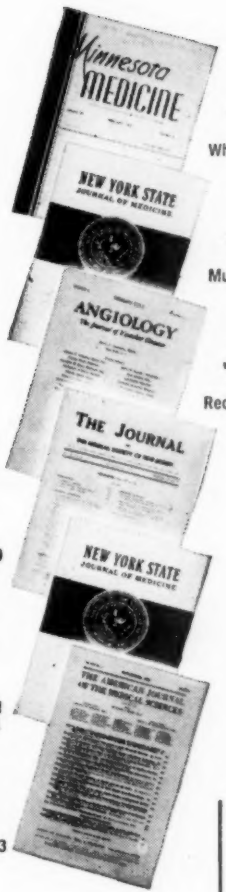

"A powerful vasodilator effect."
White, S. M.: 33:133, 1950

"Toxic effects . . . minimal."
Murphy, J. R.: 51:2407, 1951

"Safely given over prolonged periods."
Redisch, W., and Brandman, O.: 1:312, 1950

"Remarkable results in vasospastic disorders . . . Buerger's disease . . . chronic trench foot."
Redisch, W.: 46:368, 1949

"More effective . . . in arteriosclerosis obliterans. Angina of effort markedly diminished."
Richter, I. H.; Fogel, M.; and Fabricant, H.: 51:1303, 1951

"No effect upon systemic blood pressure or cardiac rate."
Crosby, R. M. N.: 225:61, 1953

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